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Concise synthesis of functionalized benzocyclobutenones

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ABSTRACT

A concise approach to access functionalized benzocyclobutenones from 3-halophenol derivatives is described. This modified synthesis employs a [2+2] cycloaddition between benzynes generated from dehydrohalogenation of aryl halides using LiTMP and acetaldehyde enolate generated from *n*-BuLi and THF, followed by oxidation of the benzocyclobutenol intermediates to provide benzocyclobutenones. The [2+2] reaction can be run on a 10-g scale with an increased yield. A number of functional groups including alkenes and alkynes are tolerated. Coupling of benzynes with ketene silyl acetals to give 8-substituted benzocyclobutenones is also demonstrated.

1. Introduction

Benzocyclobutenones are a unique class of compounds with rich reactivity, thus often serve as value building blocks for organic synthesis.[1] Ring-opening of benzocyclobutenones is known to be triggered by heat[2] or nucleophiles,[3] and also known to be facilitated by transition metals.[4] Combining further reactions of metal-carbon bonds, transition metal-mediated C–C bond cleavage of benzocyclobutenones can lead to new transformations for preparing novel structures.[5] For example, recently we have developed intramolecular couplings between benzocyclobutenones and olefins to give fused rings and spirocycles, respectively (Fig. 1).[6] A divergent approach has also been developed to access fused β-naphthols and indenes via direct and decarbonylative insertions of alkynes into benzocyclobutenones.[7] Structural motifs generated from these methodologies have been found in a number of natural products.

While these methods are potentially useful and attractive for synthesizing bioactive molecules, one key challenge is that the benzocyclobutenone substrates containing alkene or alkyne functional groups usually required more than six steps to prepare (Fig. 2). For example, we previously employed a slightly modified procedure first developed by Suzuki to access the key intermediate, 3-hydroxybenzocyclobutenone (**3**).[8] Although reliable and scalable, this synthetic route takes about six steps from resorcinol. In addition, while reagent **5** is commercially available, it is expensive and generally prepared in one step from the corresponding ester.[9] The substrates (**1** and **2**) employed in our methodologies are generally prepared with an additional step from **3** via direct alkylation or Mitsunobu reaction, thus requiring 7–8 steps total, which significantly diminished the practicality of these methodologies. Hence, to address the abovementioned challenge, a more efficient and practical synthesis of functionalized benzocyclobutenones is needed. In this article, we describe our development of a concise approach to access the substituted benzocyclobutenones, including those with alkene and alkyne moieties.

The synthesis of benzocyclobutenones is non-trial and has been an ongoing research. While a number of innovative approaches are available,[10] [2+2] cycloaddition between an aryne and a ketene equivalent still represents the most popular way to prepare benzocyclobutenones.[11] In 1982, Bisacchi and Stevens developed the first [2+2] cycloaddition to prepare benzocyclobutenones, in which the benzyne was generated from dehydrobromination of aryl bromides with sodium amide, and 1,1-dimethoxyethylene was used as the ketene equivalent.[12] While this method is widely useful, heating (75–80 °C) is generally required and preparation of 1,1-dimethoxyethylene is not convenient.[13] Consequently, Santelli, Ibrahim-Ouali and co-workers later found 1,1-dimethoxyethylene can be substituted with commercially available 2-methylene-1,3-dioxepane as the [2+2] partner albeit giving lower yields.[14] Due to the harsh conditions to generate benzynes from sodium amide, Suzuki and co-workers developed a mild procedure to synthesize benzocyclobutenones through generating the corresponding arynes via halogen-metal exchange followed by elimination of an *ortho*-triflate (vide supra, Fig. 2).[8] Another advantage of Suzuki's method is using ketene silyl acetals as the coupling partner because

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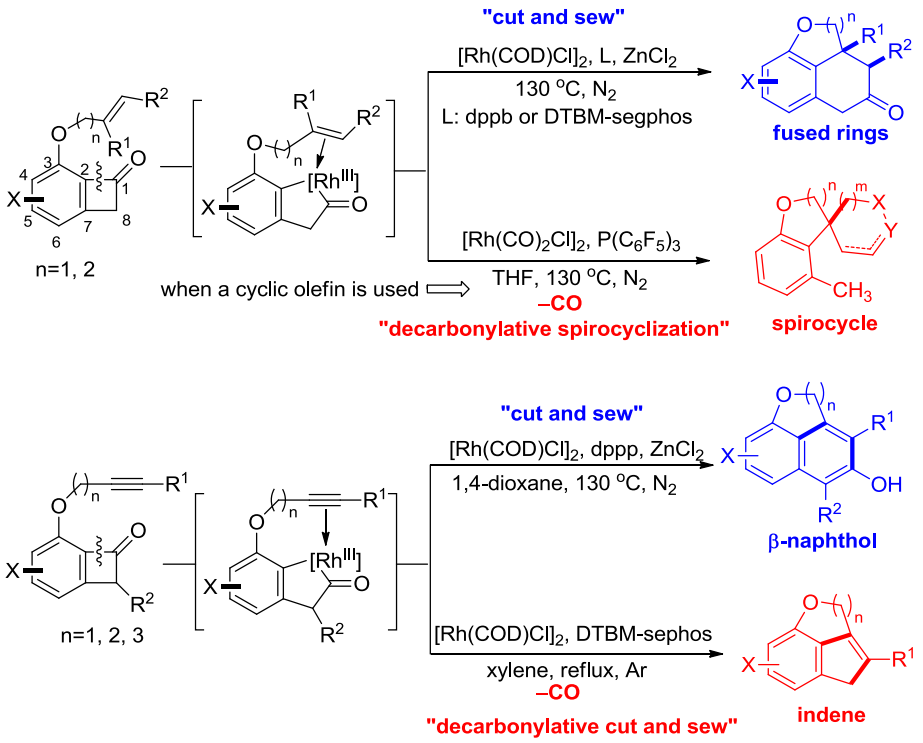


Fig. 1. Rh-catalyzed coupling reactions between benzocyclobutenones and alkenes/alkynes.

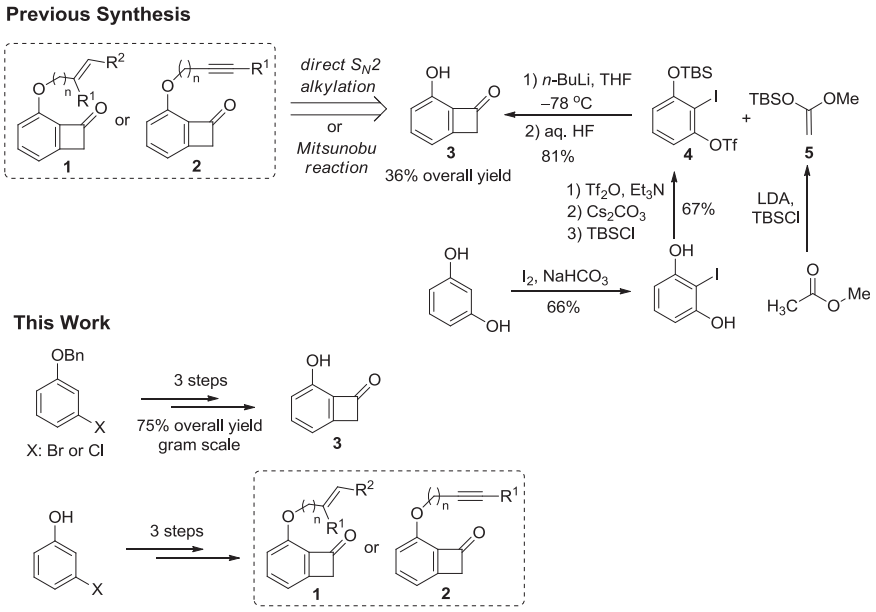


Fig. 2. Synthesis of benzocyclobutenone substrates with alkene and alkyne moieties.

they are more readily available and easier to handle than 1,1-dialkoxyethylene. Nevertheless, both *ortho*-iodo triflates and ketene silyl acetals require additional steps to prepare. Therefore, more efficient synthesis of benzocyclobutenones is still highly sought after.

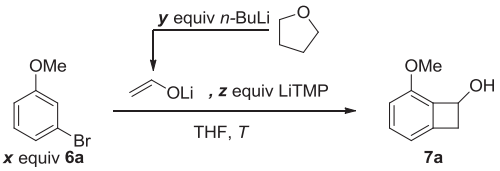
Our research was inspired by an anthracene synthesis first developed by Fleming in 1975, which involved a benzocyclobutenoxide intermediate from a [2+2] addition between benzynes [prepared from dehydrobromination of aryl bromides with LiTMP (*N*-lithio-2,2,6,6-tetramethylpiperidine)], and acetaldehyde enolates (in situ generated from THF with *n*-BuLi).[15] Olofson and co-workers later found the benzocyclobutenoxide intermediates could be trapped by various electrophiles providing synthetically useful structural motifs.[16] In contrast, utilizing this [2+2] reaction to prepare benzocyclobutenols has been much less developed likely due to the sensitivity of the benzocyclobutenoxide intermediates that can undergo reversible ring opening to give the corresponding highly reactive *o*-quinodimethanes. The work by Durst[17] and more recently by Kraus[18] demonstrated the feasibility to capture the benzocyclobutenol products using Fleming's approach, although few functional groups except methoxy groups have been examined for compatibility. We were stimulated by the simplicity of this

approach to prepare benzocyclobutenols from relatively inexpensive feedstock, i.e., aryl halides and THF, and expect subsequent oxidation[19] would provide a rapid way to access benzocyclobutenones. Hence, our study began with optimizing the reaction conditions for the synthesis of benzocyclobutenol, then investigating the influence of functional groups including alkenes and alkynes, and finally employing this approach to prepare functionalized benzocyclobutenones via subsequent alcohol oxidation.

2. Result and discussions

Initial study employed 3-bromonanisole (**6a**) as the model substrate (Table 1). LiTMP was used as the base to generate the corresponding benzyne,[20] and acetaldehyde enolate was produced in situ from *n*-BuLi and THF. While previous studies took acetaldehyde enolate as the limiting reagent,[17,18] we found higher yield of

Table 1
Selected optimization studies



Entry	*x*	*y*	*z*	*T*	Yield (%)[a]
1	2	1	2.5	−40 °C	62
2	1	2	2.5	−78 °C	70
3	1	1.5	1.2	−78 °C	71

[a] Isolated yields: yields are based on the limiting reagent.

benzocyclobutenol **7a** was obtained when aryl bromide **6a** was used as the limiting reagent (entry 2). In addition, cleaner reaction was observed when it was set up at −78 °C. Furthermore, we discovered that large excess of acetaldehyde enolate and LiTMP were not needed; use of 1.2 equiv of LiTMP and 1.5 equiv of *n*-BuLi provided benzocyclobutenol **7a** in 71% isolated yield (the highest yield reported previously is 50%[18]) (entry 3).

With the optimized conditions in hand, we next examined the aryl halide substrates with different substituents. A number of 3-halo-substitued arenes were found to be suitable substrates providing the desired benzocyclobutenols (Table 2). Subsequent oxidation with Dess–Martin periodinane (DMP)[21] afforded various functionalized benzocyclobutenones in high yields. In general, both aryl bromides and chlorides can be used as the benzyne precursor, and the bromide substrate showed higher reactivity than the corresponding chlorides. In addition, 3,4 and 3,6-disubstituted benzocyclobutenones can be obtained in high yields (entries 3, 4, 6). It is interesting to note that substrate **6h** containing two chlorides worked well giving chloro-substituted benzocyclobutenone (**8h**). While giving low yields, the OTBS-ether and dimethylaniline substrates (**6g**, **6i**, and **6j**) showed feasibility for the [2+2] cyclization. Under our conditions, 2-bromoanisole exhibited very low reactivity (entry 8). We were delighted to find that benzyl ethers were tolerated (**6c** and **6d**). Given that benzyl protecting group is more convenient to remove than a methyl group, we expect compound **6d** would be a more suitable substrate for the synthesis of key intermediate **3**. Indeed, the [2+2] cycloaddition with commercially available **6d** gave benzocyclobutenol **7c** on a 30-g scale, and the crude product can be used for next step without purification. Subsequent Moffatt–Swern oxidation[22] followed by benzyl-deprotection with $Pd(OH)_2$ and H_2 provided 3-hydroxybenzo cyclobutenone **3** in 75% overall yield on a 10-g scale over three steps (Scheme 1).

Given that the C–C activation methodologies that we previously developed[6,7] require benzocyclobutenones containing olefin or acetylene moiety, we next investigated the compatibility of C–C double and triple bonds under the benzyne/enolate [2+2] conditions. A number of alkene or alkyne-substituted 3-halophenyl ethers (**6l**–**6q**) were prepared in good to excellent yields through either direct alkylation (S_N2) or Mitsunobu reaction[23] (Table 3). To our delight, these substrates all produced benzyne and underwent [2+2] cycloaddition smoothly; subsequent oxidation provided the alkene/alkyne-tethered benzocyclobutenones in good overall yields.[24] This approach allows us to prepare the C–C activation substrates in only three steps from inexpensive 3-halophenols.

Besides acetaldehyde lithium enolate generated from THF, ketene silyl acetals were also found to be suitable coupling partners to give protected benzocyclobutenones, which can be efficiently deprotected using aqueous HF to reveal the ketones (Scheme 2).[25] One advantage of this approach is that it allows for preparation of 8-substituted benzocyclobutenones rapidly from bromoarenes. Our preliminary results indicated that 8-methyl and ethyl-substituted benzocyclobutenones can be prepared in moderate to good yields using this approach.

3. Conclusion

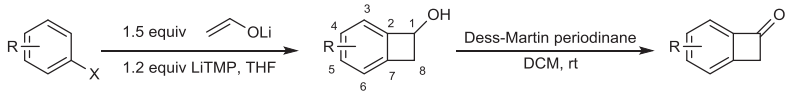
In summary, we have modified a previously reported method to synthesize benzocyclobutenone derivatives from 3-haloanisole and acetaldehyde enolate and thus developed a simpler approach to access substituted benzocyclobutenones from 3-halophenol derivatives. This reaction sequence proves to be scalable and tolerates a number of functional groups. Moreover, this approach streamlined the synthesis of our key C–C activation intermediate/substrates **1**–**3** by halving the number of steps from the previous route; thus, it makes the benzocyclobutenone/alkene and alkyne coupling methodologies more attractive. Given the ease to generate acetaldehyde enolate and the ready availability of aryl halides, we expect that this strategy will also be useful for preparing various other benzocyclobutenols and benzocyclobutenones.

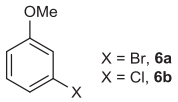
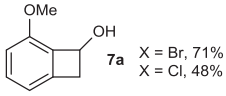
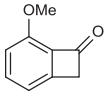
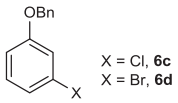
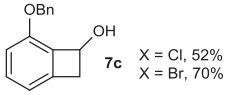
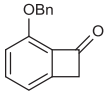
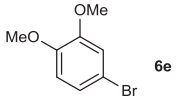
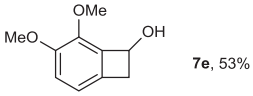
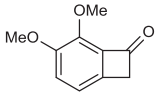
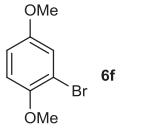
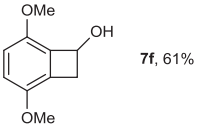
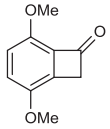
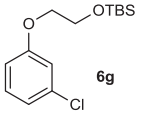
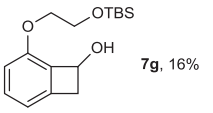
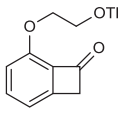
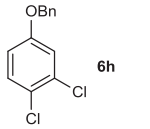
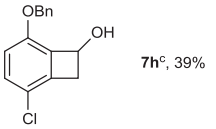
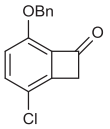
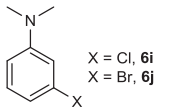
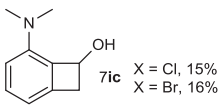
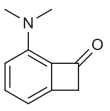
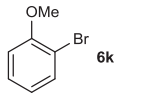
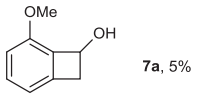
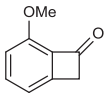
4. Experimental

4.1. General

THF was purchased from Fischer scientific, dried by filtration through a Pure-Solv MD-5 Solvent Purification System (Innovative Technology) and was distilled freshly over sodium. DCM was dried by filtration through a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). All reagents were reagent grade and were purchased and used without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F_{254}, EMD chemical). High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as *m*/*z* (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M-H]^-$ or [M]. Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film technique. Nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded with a Varian Gemini (400 MHz, ^1H at 400 MHz, ^{13}C at 100 MHz). Unless otherwise noted, all spectra were acquired in $CDCl_3$. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, δ=0.00 ppm) and are referenced to residual solvent ($CDCl_3$, δ=7.26 ppm (^1H) and 77.16 ppm (^{13}C)). Coupling constants were reported in Hertz (Hz). Data for ^1H NMR spectra were reported as follows: chemical shift (ppm, referenced to protium; s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, dd=doublet of doublets, td=triplet of doublets, ddd=doublet of doublet of doublets, m=multiplet, coupling constant (Hz), and integration). Compounds **6a**, **6b**, **6d**, **6e**, **6f**,

Table 2
A two-step benzocyclobutenone synthesis: substrates with different substituents



Entry	Substrate	[2+2] Product[a]	Oxidation product[b]
1	 X = Br, **6a** X = Cl, **6b**	 **7a** X = Br, 71% X = Cl, 48%	 **8a**, 98%
2	 X = Cl, **6c** X = Br, **6d**	 **7c** X = Cl, 52% X = Br, 70%	 **8c**, 96%
3	 **6e**	 **7e**, 53%	 **8e**, 88%
4	 **6f**	 **7f**, 61%	 **8f**, 95%
5	 **6g**	 **7g**, 16%	 **8g**[d], 85%
6	 **6h**	 **7h**[c], 39%	 **8h**, 98%
7	 X = Cl, **6i** X = Br, **6j**	 **7ic** X = Cl, 15% X = Br, 16%	 **8i**[d], 21%
8	 **6k**	 **7a**, 5%	 **8a**, 98%

[a]Otherwise noted, general procedure C was applied.
[b]Otherwise noted, general procedure F was applied.
[c]General procedure D was applied.
[d]General procedure G was applied.

Scheme 1. Synthesis of 3-hydroxybenzocyclobentenone **3**.

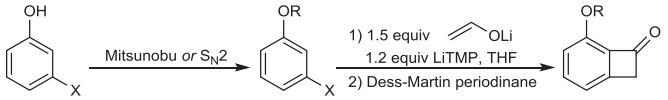
6i, **6j**, and **6k** are commercially available and used as purchased without purification. **6c**,[26] **6h**,[27] **6r**,[28] and **6v**[29] are known compounds from literature.

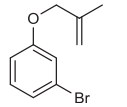
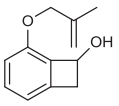
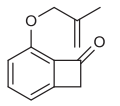
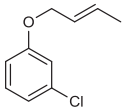
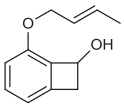
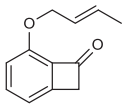
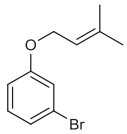
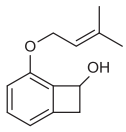
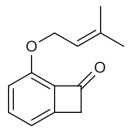
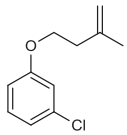
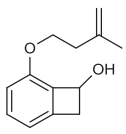
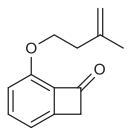
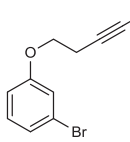
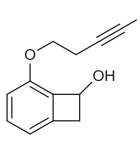
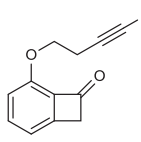
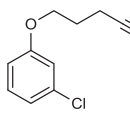
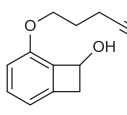
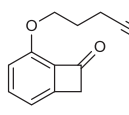
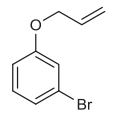
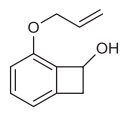
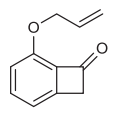
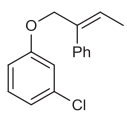
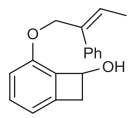
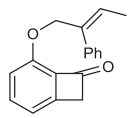
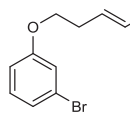
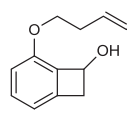
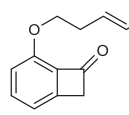
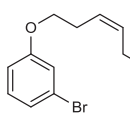
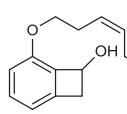
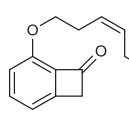
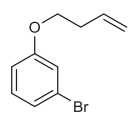
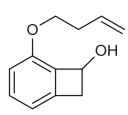
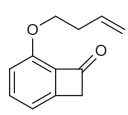
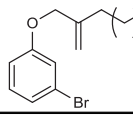
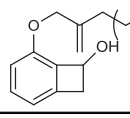
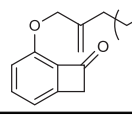
4.2. General procedure A: Mitsunobu reaction

To a 50 mL flamed-dried flask equipped with a stir bar and a rubber septum were added phenol derivatives (6 mmol, 1 equiv), PPh_3 (6.6 mmol, 1.1 equiv), corresponding alcohols (6.6 mmol, 1.1 equiv), and THF (20 mL). With stirring, DIAD (6.6 mmol, 1.1 equiv) was added dropwise. Upon completion, the reaction was heated to 60 °C overnight. The reaction mixture was then concentrated under vacuum and directly purified via flash chromatography on silica gel to afford the following compounds.

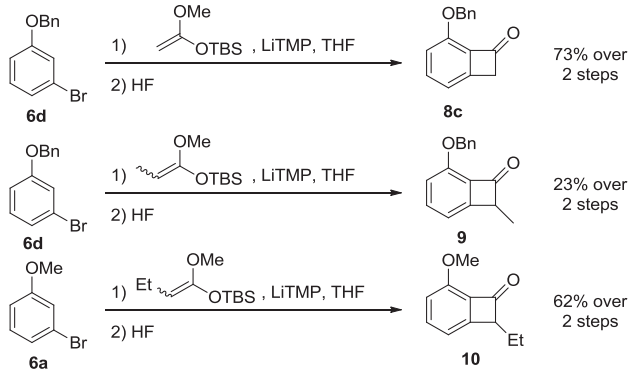
*4.2.1. tert-Butyl(2-(3-chlorophenoxy)ethoxy)dimethylsilane (**6g**).* Compound **6g** was obtained in 95% yield as a colorless oil (652 mg) from 3-chlorophenol and 2-((*tert*-butyldimethylsilyl)-

Table 3
Substrates with alkene and alkyne functional groups



Entry	Substrate	[2+2] Product[a]	Oxidation product[b]
1	 95%, **6l**[c]	 61%, **7l**	 98%, **8l**
2	 91%, **6m**[d]	 64%, **7m**	 94%, **8m**
3	 98%, **6n**[c]	 56%, **7n**	 77%, **8n**
4	 96%, **6o**[d]	 66%, **7o**	 98%, **8o**
5	 76%, **6p**[d]	 51%, **7p**	 93%, **8p**
6	 98%, **6q**[d]	 32%, **7q**	 86%, **8q**
7	 **6r**	 17%, **7r**	 74%, **8r**
8	 93%, **6s**[d]	 60%, **7s**	 93%, **8s**
9	 94%, **6t**[d]	 25%, **7t**	 94%, **8t**
10	 81%, **6u**[d]	 27%, **7u**	 97%, **8u**
11	 **6v**	 27%, **7v**	 92%, **8v**
12	 98%, **6w**[d]	 48%, **7w**	 86%, **8w**

[a]General procedure C was applied.
[b]General procedure F was applied.
[c]General procedure B was applied.
[d]General procedure A was applied.



Scheme 2. Synthesis of 8-substituted benzocyclobutenones through coupling with ketene silyl acetals.

oxy)ethan-1-ol, R_f=0.7 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J=8.2 Hz, 1H), 6.94–6.90 (m, 2H), 6.82–6.77 (m, 1H), 4.02 (t, J=4.9 Hz, 2H), 3.96 (t, J=4.9 Hz, 2H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (s), 134.8 (s), 130.1 (s), 120.8 (s), 114.9 (s), 113.1 (s), 69.5 (s), 61.9 (s), 25.9 (s), 18.4 (s), −5.4 (s). IR: ν 2955, 2929, 2857, 2360, 2342, 1596, 1471, 1285, 1252, 1135, 1106, 1072, 836, 776, 680 cm^{-1}. HRMS calcd for $C_{14}H_{23}ClNaO_2Si^+$ $[M+Na]^+$: 309.1048, found: 309.1038.

*4.2.2. (E)-1-(But-2-en-1-yloxy)-3-chlorobenzene (**6m**).* Compound **6m** was obtained in 91% yield as colorless oil (1.67 g) from 3-chlorophenol and 2-buten-1-ol (*cis*:*trans*=1:19), R_f=0.3 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (ddd, J=8.3, 7.8, 0.4 Hz, 1H), 6.93–6.87 (m, 2H), 6.78 (ddd, J=8.4, 2.4, 1.0 Hz, 1H), 5.90–5.80 (m, 1H), 5.74–5.65 (m, 1H), 4.44–4.40 (m, 2H), 1.75 (ddd, J=6.4, 2.7, 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (s), 134.8 (s), 131.0 (s), 130.1 (s), 125.5 (s), 120.8 (s), 115.0 (s), 113.3 (s), 68.9 (s), 17.9 (s). IR: ν 2968, 2094, 1636, 1596, 1477, 1377, 1306, 1282, 1227, 1009, 965, 765, 680 cm^{-1}. HRMS calcd for $C_{10}H_{11}ClO$ [M]: 182.0498, found: 182.0497.

*4.2.3. 1-Chloro-3-((3-methylbut-3-en-1-yl)oxy)benzene (**6o**).* Compound **6o** was obtained in 96% yield as colorless oil (1.90 g) from 3-chlorophenol and 3-methyl-3-buten-1-ol, R_f=0.3 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.14 (m, 1H), 6.93–6.87 (m, 2H), 6.80–6.75 (m, 1H), 4.85–4.82 (m, 1H), 4.81–4.76 (m, 1H), 4.04 (t, J=6.8 Hz, 2H), 2.48 (t, J=6.8 Hz, 2H), 1.79 (d, J=0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (s), 141.9 (s), 134.8 (s), 130.1 (s), 120.8 (s), 114.9 (s), 113.1 (s), 112.1 (s), 66.6 (s), 37.0 (s), 22.8 (s). IR: ν 3077, 2936, 1651, 1679, 1470, 1428, 1387, 1263, 1231, 1071, 1042, 864, 840, 764 cm^{-1}. HRMS calcd for $C_{11}H_{13}ClO$ [M]: 196.0655, found: 196.0656.

*4.2.4. 1-Bromo-3-(hex-3-yn-1-yloxy)benzene (**6p**).* Compound **6p** was obtained in 76% yield as a light yellow oil (1.15 g) from 3-bromophenol and 3-hexyn-1-ol, R_f=0.8 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.05 (m, 3H), 6.85–6.80 (m, 1H), 4.01 (t, J=7.2 Hz, 2H), 2.61 (t, J=7.2, 2.4 Hz, 2H), 2.16 (qt, J=7.5, 2.4 Hz, 2H), 1.11 (t, J=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (s), 130.5 (s), 124.0 (s), 122.8 (s), 117.9 (s), 113.6 (s), 83.6 (s), 74.8 (s), 66.8 (s), 19.7 (s), 14.1 (s), 12.4 (s). IR: ν 2108, 1652, 1468, 1284, 1229, 1036 cm^{-1}. HRMS calcd for $C_{12}H_{13}BrO$ [M]: 252.0150, found: 252.0154.

*4.2.5. 1-Chloro-3-((5-phenylpent-4-yn-1-yl)oxy)benzene (**6q**).* Compound **6q** was obtained in 98% yield as a colorless oil (836 mg) from 3-chlorophenol and 5-phenylpent-4-yn-1-ol, R_f=0.8 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2H), 7.29–7.24 (m, 3H), 7.18 (t, J=8.4 Hz, 1H), 6.93–6.90 (m, 2H), 6.80 (ddd, J=8.4, 2.4, 1.0 Hz, 1H), 4.09 (t, J=6.1 Hz, 2H), 2.61 (t, J=6.9 Hz, 2H), 2.10–2.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (s), 134.8 (s), 131.6 (s), 130.2 (s), 128.2 (s), 127.7 (s), 123.6 (s), 120.8 (s), 114.9 (s), 113.1 (s), 88.8 (s), 81.3 (s), 66.6 (s), 28.3 (s), 16.1 (s). IR: ν 2964, 2919, 1647, 1605, 1583, 1480, 1469, 1274, 1140, 1054, 893, 782 cm^{-1}. HRMS calcd for $C_{17}H_{15}ClO$ [M]: 270.0811, found: 270.0809.

*4.2.6. (E)-1-Chloro-3-((2-phenylbut-2-en-1-yl)oxy)benzene (**6s**).* Compound **6s** was obtained in 93% yield as a colorless oil (957.9 mg) from 3-chlorophenol and (*E*)-2-phenylbut-2-en-1-ol,[30] R_f=0.8 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.33 (m, 2H), 7.31–7.22 (m, 3H), 7.16 (td, J=8.4, 0.6 Hz, 1H), 6.92–6.88 (m, 2H), 6.78 (ddt, J=8.3, 2.2, 1.0 Hz, 1H), 6.00–5.91 (m, 1H), 4.65 (dd, J=2.2, 1.0 Hz, 2H), 1.67 (dt, J=7.0, 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (s), 138.2 (s), 136.6 (s), 134.9 (s), 130.3 (s), 128.9 (s), 128.5 (s), 127.4 (s), 126.4 (s), 121.1 (s), 115.5 (s), 113.5 (s), 73.1 (s), 14.8 (s). IR: ν 3055.89, 3022.11, 2984.13, 2915.73, 2858.38, 1594.55, 1479.73, 1375.20, 1306.56, 1282.56, 1243.84, 1225.69, 1090.91, 1071.71, 1008.11, 893.99, 861.23, 838.07, 764.71, 701.87, 680.44 cm^{-1}. HRMS calcd for $C_{16}H_{14}ClO$ [M]: 257.0733, found: 257.0738.

*4.2.7. (E)-1-Bromo-3-(hex-3-en-1-yloxy)benzene (**6t**).* Compound **6t** was obtained in 94% yield as a colorless oil (1.1948 g) from 3-bromophenol and (*E*)-hex-3-en-1-ol, R_f=0.8 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, J=8.3 Hz, 1H), 7.06–7.02 (m, 2H), 6.81 (ddd, J=8.2, 2.2, 1.3 Hz, 1H), 5.68–5.38 (m, 2H), 3.92 (t, J=6.9 Hz, 2H), 2.52–2.39 (m, 2H), 2.10–1.96 (m, 2H), 0.97 (t, J=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (s), 135.1 (s), 130.5 (s), 124.3 (s), 123.7 (s), 122.9 (s), 117.9 (s), 113.6 (s), 68.1 (s), 32.5 (s), 25.8 (s), 13.9 (s). IR: ν 2962.45, 2931.60, 2872.51, 1589.33, 1572.77, 1477.33, 1467.23, 1423.67, 1387.51, 1304.40, 1284.04, 1243.85, 1228.25, 1064.51, 1030.13, 991.36, 967.39, 864.47, 763.80, 680.07 cm^{-1}. HRMS calcd for $C_{12}H_{15}BrO$ [M]: 254.0306, found: 254.0301.

*4.2.8. (Z)-1-Bromo-3-(hex-3-en-1-yloxy)benzene (**6u**).* Compound **6u** was obtained in 81% yield as a colorless oil (1.0335 g) from 3-bromophenol and (*Z*)-hex-3-en-1-ol, R_f=0.8 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.08 (m, 1H), 7.07–7.05 (m, 1H), 7.04–7.02 (m, 1H), 6.80 (ddd, J=8.2, 2.4, 1.2 Hz, 1H), 5.57–5.34 (m, 2H), 3.91 (t, J=6.9 Hz, 2H), 2.55–2.47 (m, 2H), 2.13–2.02 (m, 2H), 0.97 (t, J=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (s), 134.5 (s), 130.5 (s), 123.9 (s), 123.70 (s), 122.9 (s), 117.8 (s), 113.5 (s), 67.7 (s), 27.3 (s), 20.8 (s), 14.4 (s). IR: ν 3010.01, 2963.14, 2931.95, 2873.44, 1590.34, 1573.28, 1477.45, 1467.58, 1423.93, 1384.86, 1324.35, 1243.67, 1228.67, 1064.73, 1031.03, 928.69, 855.47, 845.36, 764.17, 726.61, 680.08 cm^{-1}. HRMS calcd for $C_{12}H_{15}BrO$ [M]: 254.0306, found: 254.0304.

*4.2.9. 1-Bromo-3-((2-methylenedecyl)oxy)benzene (**6w**).* Compound **6w** was obtained in 98% yield as a colorless oil (1.0335 g) from 3-bromophenol and 2-methylenedecan-1-ol,[31] R_f=0.95 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J=10.9, 5.5 Hz, 1H), 7.10–7.07 (m, 2H), 6.86 (ddd, J=8.1, 2.4, 1.2 Hz, 1H), 5.12 (d, J=1.3 Hz, 1H), 5.01 (d, J=1.3 Hz, 1H), 4.44 (s, 2H), 2.18–2.10 (m, 2H), 1.49 (dt, J=14.9, 7.4 Hz, 2H), 1.38–1.22 (m, 10H), 0.89 (t, J=6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (s), 144.4 (s), 130.5 (s), 123.9 (s), 122.9 (s), 118.2 (s), 113.6 (s), 112.0 (s), 71.0 (s), 33.2 (s), 32.1 (s), 29.7 (s), 29.6 (s), 29.5 (s), 27.7 (s), 22.9 (s), 14.3 (s). IR: ν 2925.69, 2854.50, 1653.98, 1589.36, 1573.78, 1475.15, 1303.47, 1283.61, 1224.44, 1020.29, 903.21, 763.62, 679.35 cm^{-1}. HRMS calcd for $C_{17}H_{25}OBr$ [M]: 324.1089, found: 324.1086.

4.3. General procedure B: S_N2 reaction

To a 100 mL flask equipped with a stir bar were added 3-bromophenol (10 mmol, 1 equiv), K_2CO_3 (50 mmol, 5 equiv), KI (30 mmol, 3 equiv) corresponding allylic halide (25 mmol, 2.5 equiv), and acetone (30 mL). The reaction was then heated to

reflux for ca. 12 h before quenching with aqueous NH_4Cl. The aqueous phase was extracted with ethyl acetate (30 mL×3). The combined organic extract was concentrated under reduced pressure and purified by column chromatography on silica gel to afford the following compounds.

*4.3.1. 1-Bromo-3-((2-methylallyl)oxy)benzene (**6l**).* Compound **6l** was obtained in 95% yield as a colorless oil (2.16 g) from 3-bromophenol and 3-chloro-2-methyl-1-propene, R_f=0.2 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.04 (m, 3H), 6.84 (ddd, J=8.1, 2.4, 1.2 Hz, 1H), 5.09–5.05 (m, 1H), 5.00–4.97 (m, 1H), 4.40 (s, 2H), 1.83–1.79 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (s), 140.3 (s), 130.5 (s), 123.9 (s), 122.7 (s), 118.0 (s), 113.7 (s), 113.0 (s), 71.9 (s), 19.3 (s). IR: ν 2340, 1683, 1506, 1436, 1424, 1222, 1017 cm^{-1}. HRMS calcd for $C_{10}H_{11}BrO$ [M]: 225.9993, found: 225.9994.

*4.3.2. 1-Bromo-3-((3-methylbut-2-en-1-yl)oxy)benzene (**6n**).* Compound **6n** was obtained in 98% yield as a colorless oil (2.36 g) from 3-bromophenol and 3,3-dimethylallyl bromide, R_f=0.2 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.08 (m, 1H), 7.07–7.02 (m, 2H), 6.83 (ddd, J=8.2, 2.3, 1.1 Hz, 1H), 5.49–5.42 (m, 1H), 4.47 (d, J=6.8 Hz, 2H), 1.76 (d, J=22.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (s), 138.7 (s), 130.5 (s), 123.6 (s), 122.7 (s), 119.1 (s), 117.8 (s), 113.8 (s), 65.0 (s), 25.8 (s), 18.2 (s). IR: ν 2914, 1587, 1475, 1383, 1283, 1224, 1064, 1000, 881, 764, 680 cm^{-1}. HRMS calcd for $C_{11}H_{13}BrO$ [M]: 240.0150, found: 240.0150.

4.4. General procedure C: [2+2] coupling I

To a 100 mL flamed-dried flask equipped with stir bar and a nitrogen-filled balloon was added THF (20 mL). The system was cooled to 0 °C with an ice-water bath before *n*-BuLi (2.5 M in hexane, 6 mmol, 1.5 equiv) was added dropwise. Upon completion, the system was warmed to rt and stirred for 16 h under nitrogen atmosphere. At the same time, to a 30 mL flamed-dried flask equipped with a stir bar and a nitrogen-filled balloon were added 2,2,6,6-tetramethylpiperidine (4.8 mmol, 1.2 equiv) and THF (12 mL). After cooling to 0 °C with an ice-water bath, *n*-BuLi (2.5 M in hexane, 4.8 mmol, 1.2 equiv) was added dropwise and the reaction was stirred at 0 °C for 0.5 h. The previous 100 mL flask was cooled to −78 °C with an acetone-dry ice bath and benzyne precursor (4 mmol, 1.0 equiv) in THF (5 mL) was added before in situ generated lithium tetramethylpiperidine was added dropwise. The reaction was monitored by TLC and was quenched by adding aqueous NH_4Cl. The mixture was then warmed to rt and H_2O (30 mL) was added. The mixture was extracted with ethyl acetate (30 mL×3), washed with brine, and dried with Na_2SO_4. The combined organic extract was concentrated under reduced pressure and purified by column chromatography on silica gel to afford the following compounds.

*4.4.1. 5-Methoxybicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7a**).* Compound **7a**[18] (CAS No.: 66947-61-3) was obtained as a white solid from **6a** in 71% yield (425 mg) and **6b** in 48% yield (287 mg), R_f=0.15 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J=8.3, 7.3 Hz, 1H), 6.75–6.69 (m, 2H), 5.36 (ddd, J=9.6, 4.5, 1.8 Hz, 1H), 3.97 (s, 3H), 3.60 (dd, J=14.5, 4.5 Hz, 1H), 3.00 (ddt, J=14.5, 1.7, 0.7 Hz, 1H), 2.29 (d, J=9.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (s), 144.1 (s), 131.3 (s), 130.9 (s), 115.6 (s), 113.8 (s), 70.7 (s), 56.9 (s), 42.5 (s).

*4.4.2. 5-(Benzyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7c**).* Compound **7c** was obtained as a white solid from **6c** in 52% yield (470 mg) and **6d** in 70% yield (637 mg), R_f=0.2 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.21 (m, 6H), 6.81 (dd, J=8.5, 0.7 Hz, 1H), 6.74 (dd, J=7.2, 0.5 Hz, 1H), 5.32 (dd, J=39.8, 12.2 Hz, 2H), 5.22 (ddd, J=9.6, 4.6, 1.9 Hz, 1H), 3.58 (dd, J=14.5, 4.6 Hz, 1H), 3.00 (ddt, J=14.5, 1.7, 0.8 Hz, 1H), 2.21 (d, J=9.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (s), 144.0 (s), 137.4 (s), 131.4 (s), 131.0 (s), 128.5 (s), 127.9 (s), 127.2 (s), 115.9 (s), 114.9 (s), 71.1 (s), 70.8 (s), 42.4 (s). IR: ν 3071, 2956, 2929, 1719, 1600, 1581, 1475, 1390, 1350, 1265, 1155, 1108, 1032, 845 cm^{-1}. HRMS calcd for $C_{15}H_{14}NaO_2^+$ [M+Na]$^+$: 249.0891, found: 249.0889. Mp (°C): 81–83.

*4.4.3. 4,5-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7e**).* Compound **7e**[16b] (CAS No.: 144493-71-0) was obtained in 53% yield as a white solid (385 mg) from **6e**, R_f=0.1 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J=7.7 Hz, 1H), 6.64 (dt, J=7.7, 0.9 Hz, 1H), 5.33 (ddd, J=10.3, 4.7, 1.9 Hz, 1H), 4.10 (s, 3H), 3.82 (s, 3H), 3.56 (ddd, J=14.3, 4.7, 0.9 Hz, 1H), 2.94 (ddd, J=14.3, 1.9, 1.0 Hz, 1H), 2.18 (d, J=10.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6 (s), 144.5 (s), 134.7 (s), 130.6 (s), 115.5 (s), 114.2 (s), 70.4 (s), 58.1 (s), 56.5 (s), 41.8 (s).

*4.4.4. 2,5-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**7f**).* Compound **7f** was obtained in 61% yield as a pale solid (437 mg) from **6f**, R_f=0.1 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, J=9.0 Hz, 1H), 6.65 (d, J=9.0 Hz, 1H), 5.32 (ddd, J=9.0, 4.4, 1.4 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.71 (ddd, J=13.9, 4.5, 0.4 Hz, 1H), 3.10 (ddd, J=14.0, 1.8, 0.7 Hz, 1H), 2.33 (d, J=9.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5 (s), 148.4 (s), 132.2 (s), 126.6 (s), 116.7 (s), 115.0 (s), 70.4 (s), 57.0 (s), 56.5 (s), 41.7 (s). IR: ν 3446, 2947, 2837, 1646, 1590, 1505, 1464, 1436, 1258, 1142, 1109, 1077, 1047, 999, 811 cm^{-1}. HRMS calcd for $C_{10}H_{12}NaO_3^+$ [M+H]$^+$: 203.0679, found: 203.0675. Mp (°C): 72–75.

*4.4.5. 5-(2-((tert-Butyldimethylsilyl)oxy)ethoxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**7g**).* Compound **7g** was obtained in 16% yield as a pale solid (47 mg) from **6g**, R_f=0.2 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.16 (m, 1H), 6.70 (dd, J=7.8, 3.3 Hz, 2H), 5.32 (dd, J=11.0, 6.3 Hz, 1H), 4.50 (ddd, J=11.0, 5.7, 5.0 Hz, 1H), 4.17 (dt, J=11.2, 4.2 Hz, 1H), 3.96 (t, J=4.6 Hz, 2H), 3.54 (dd, J=14.3, 4.5 Hz, 1H), 3.26 (d, J=8.3 Hz, 1H), 2.99 (d, J=14.4 Hz, 1H), 0.86 (s, 9H), 0.04 (d, J=23.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (s), 143.9 (s), 131.2 (s), 130.4 (s), 115.6 (s), 114.7 (s), 70.5 (s), 70.1 (s), 63.2 (s), 42.2 (s), 25.8 (s), 18.4 (s), −5.4 (d, J=2.9 Hz). IR: ν 3223, 2955, 2929, 2857, 1605, 1583, 1475, 1453, 1263, 1130, 1097, 1064, 949, 832, 775 cm^{-1}. HRMS calcd for $C_{16}H_{24}NaO_3Si^+$ [M+Na]$^+$: 315.1543, found: 315.1534. Mp (°C): 49–51.

*4.4.6. 5-((2-Methylallyl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7l**).* Compound **7l** was obtained in 61% yield as a yellow solid (465 mg) from **6l**, R_f=0.1 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J=8.3, 7.3 Hz, 1H), 6.75 (dd, J=8.5, 0.7 Hz, 1H), 6.71 (d, J=6.5 Hz, 1H), 5.28 (ddd, J=10.0, 4.5, 1.8 Hz, 1H), 5.05 (td, J=2.4, 1.6 Hz, 1H), 4.94 (dt, J=2.7, 1.3 Hz, 1H), 4.65 (q, J=13.1 Hz, 2H), 3.57 (dd, J=14.5, 4.6 Hz, 1H), 2.98 (ddt, J=14.5, 1.7, 0.8 Hz, 1H), 2.16 (d, J=9.7 Hz, 1H), 1.81 (d, J=0.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (s), 143.9 (s), 141.3 (s), 131.3 (s), 130.8 (s), 115.7 (s), 114.7 (s), 112.0 (s), 72.7 (s), 70.8 (s), 42.4 (s), 19.3 (s). IR: ν 3286, 2919, 1602, 1582, 1475, 1384, 1268, 1261, 1105, 1045, 900 cm^{-1}. HRMS calcd for $C_{12}H_{14}NaO_2^+$ [M+Na]$^+$: 213.0891, found: 213.0893. Mp (°C): 47–49.

*4.4.7. (E)-5-(But-2-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7m**).* Compound **7m** was obtained in 64% yield as a white solid (490 mg) from **6m**, R_f=0.2 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J=8.3, 7.3 Hz, 1H), 6.75–6.69 (m, 2H), 5.91–5.80 (m, 1H), 5.76–5.66 (m, 1H), 5.30 (ddd, J=9.6, 4.5, 1.7 Hz, 1H), 4.76–4.58 (m, 2H), 3.57 (dd, J=14.4, 4.6 Hz, 1H), 3.06–2.90 (m, 1H), 2.23 (d, J=9.7 Hz, 1H), 1.73 (dd, J=6.4, 1.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (s), 144.0 (s), 131.3 (s), 130.9 (s), 130.3 (s),

126.3 (s), 115.6 (s), 114.6 (s), 70.9 (s), 70.0 (s), 42.4 (s), 17.9 (s). IR: ν 2956, 1653, 1603, 1582, 1457, 1262, 1137, 1106, 1046, 965, 775 cm^{-1}. HRMS calcd for $C_{12}H_{14}NaO_2$ $[M+Na]^+$: 213.0891, found: 213.0888. Mp (°C): 78–80.

*4.4.8. 5-((3-Methylbut-2-en-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7n**).* Compound **7n** was obtained in 56% yield as a light yellow solid (460 mg) from **6n**, R_f=0.2 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.17 (m, 1H), 6.74–6.68 (m, 2H), 5.48 (t, J=6.8 Hz, 1H), 5.32 (ddd, J=14.4, 8.8, 5.6 Hz, 1H), 4.74 (ddd, J=65.1, 11.5, 6.8 Hz, 2H), 3.58 (dd, J=14.4, 4.5 Hz, 1H), 3.02–2.95 (m, 1H), 2.23 (d, J=9.7 Hz, 1H), 1.76 (d, J=17.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (s), 144.0 (s), 138.4 (s), 131.3 (s), 131.0 (s), 119.9 (s), 115.5 (s), 114.7 (s), 71.0 (s), 66.1 (s), 42.4 (s), 25.8 (s), 18.2 (s). IR: ν 2967, 2925, 1605, 1582, 1469, 1384, 1251, 1199, 1043, 976, 767 cm^{-1}. HRMS calcd for $C_{13}H_{16}NaO_2^+$ $[M+Na]^+$: 227.1048, found: 227.1044. Mp (°C): 60–62.

*4.4.9. 5-((3-Methylbut-3-en-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7o**).* Compound **7o** was obtained in 66% yield as a white solid (661 mg) from **6o**, R_f=0.1 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J=8.8, 7.1 Hz, 1H), 6.73–6.70 (m, 1H), 6.69 (s, 1H), 5.32 (ddd, J=9.7, 4.5, 1.8 Hz, 1H), 4.84–4.81 (m, 1H), 4.80–4.78 (m, 1H), 4.33 (ddt, J=55.1, 9.7, 6.8 Hz, 2H), 3.59 (dd, J=14.5, 4.5 Hz, 1H), 2.99 (ddt, J=14.5, 1.7, 0.8 Hz, 1H), 2.47 (t, J=6.8 Hz, 2H), 2.15 (d, J=9.7 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (s), 144.0 (s), 142.3 (s), 131.3 (s), 130.9 (s), 115.5 (s), 114.6 (s), 111.9 (s), 70.9 (s), 67.8 (s), 42.5 (s), 37.4 (s), 22.9 (s). IR: ν 2964, 2919, 1647, 1606, 1469, 1402, 1274, 1140, 1108, 1054, 893, 765 cm^{-1}. HRMS calcd for $C_{13}H_{16}NaO_2^+$ $[M+Na]^+$: 227.1048 found: 227.1047. Mp (°C): 61–63.

*4.4.10. 5-(Hex-3-yn-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7p**).* Compound **7p** was obtained in 51% yield as a light yellow solid (439 mg) from **6p**, R_f=0.1 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J=8.4, 7.3 Hz, 1H), 6.72 (dd, J=7.8, 4.0 Hz, 2H), 5.33 (ddd, J=9.4, 4.5, 1.8 Hz, 1H), 4.37–4.18 (m, 2H), 3.58 (dd, J=14.4, 4.6 Hz, 1H), 2.99 (ddt, J=14.5, 1.7, 0.8 Hz, 1H), 2.64–2.58 (m, 2H), 2.28 (d, J=9.4 Hz, 1H), 2.15 (qt, J=7.5, 2.4 Hz, 2H), 1.09 (t, J=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (s), 144.0 (s), 131.3 (s), 130.9 (s), 115.8 (s), 114.6 (s), 83.4 (s), 75.3 (s), 70.8 (s), 67.8 (s), 42.4 (s), 20.1 (s), 14.1 (s), 12.41 (s). IR: ν 2106, 1645, 1466, 1259, 1140, 1051, 770 cm^{-1}. HRMS calcd for $C_{14}H_{16}NaO_2$ $[M+Na]^+$: 239.1048, found: 239.1045. Mp (°C): 42–45.

*4.4.11. 5-((5-Phenylpent-4-yn-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7q**).* Compound **7q** was obtained in 32% yield as a white solid (176 mg) from **6q**, R_f=0.2 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.16 (m, 6H), 6.75–6.67 (m, 2H), 5.33 (ddd, J=9.7, 4.5, 1.8 Hz, 1H), 4.36 (ddt, J=51.3, 9.8, 6.1 Hz, 2H), 3.58 (dd, J=14.5, 4.6 Hz, 1H), 3.04–2.89 (m, 1H), 2.61 (t, J=7.0 Hz, 2H), 2.20 (d, J=9.7 Hz, 1H), 2.13–1.97 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (s), 144.1 (s), 131.5 (s), 131.3 (s), 130.9 (s), 128.2 (s), 127.6 (s), 123.7 (s), 115.6 (s), 114.6 (s), 89.2 (s), 81.1 (s), 70.9 (s), 67.8 (s), 42.5 (s), 28.8 (s), 16.1 (s). IR: ν 2919, 2359, 2339, 1384, 1267, 1261, 1051, 743, 692, 668 cm^{-1}. HRMS calcd for $C_{19}H_{18}NaO_2^+$ $[M+Na]^+$: 301.1204, found: 301.1200. Mp (°C): 87–89.

*4.4.12. 5-(Allyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7r**).* Compound **7r** was obtained in 17% yield as a light yellow oil (30.1 mg) from **6r**, R_f=0.2 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J=8.3, 7.2 Hz, 1H), 6.74 (dd, J=10.8, 7.8 Hz, 2H), 6.05 (ddt, J=17.3, 10.4, 5.1 Hz, 1H), 5.40 (ddd, J=17.3, 3.3, 1.6 Hz, 1H), 5.32–5.21 (m, 2H), 4.87–4.64 (m, 2H), 3.58 (dd, J=14.5, 4.6 Hz, 1H), 3.05–2.93 (m, 1H), 2.47 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (s), 144.0 (s), 133.6 (s), 131.4 (s), 130.8 (s), 117.2 (s), 115.8 (s), 114.7 (s), 70.8 (s), 69.9 (s), 42.4 (s). IR: ν 3331.28, 2925.33, 1604.11, 1584.10, 1474.30, 1198.14, 1139.22, 1044.28, 770.46 cm^{-1}. HRMS calcd for $C_{11}H_{12}O_2$ [M]: 176.0837, found: 176.0834.

*4.4.13. (E)-5-((2-Phenylbut-2-en-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7s**).* Compound **7s** was obtained in 60% yield as colorless oil (158.9 mg) from **6s**, R_f=0.1 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.26 (m, 5H), 7.26–7.19 (m, 1H), 6.75 (dd, J=13.3, 7.8 Hz, 2H), 6.00 (q, J=6.9 Hz, 1H), 5.28 (d, J=12.1 Hz, 1H), 4.94 (dd, J=52.3, 12.0 Hz, 2H), 3.55 (dd, J=14.4, 4.5 Hz, 1H), 2.96 (d, J=14.4 Hz, 1H), 2.69 (s, 1H), 1.72 (d, J=6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (s), 144.0 (s), 138.3 (s), 137.2 (s), 131.3 (s), 131.1 (s), 128.8 (s), 128.2 (s), 127.1 (s), 125.9 (s), 115.7 (s), 114.8 (s), 74.1 (s), 70.7 (s), 42.3 (s), 14.7 (s). IR: ν 3371.38, 3057.22, 2924.24, 1603.75, 1582.78, 1493.84, 1473.32, 1377.93, 1258.18, 1197.55, 1179.16, 1140.54, 1088.88, 1042.44, 980.88, 912.35, 768.85, 728.36, 702.35 cm^{-1}. HRMS calcd for $C_{18}H_{18}NaO_2^+$ $[M+Na]^+$: 289.1199, found: 289.1200.

*4.4.14. (E)-5-(Hex-3-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7t**).* Compound **7t** was obtained in 25% yield as light yellow solid (54.2 mg) from **6t**, R_f=0.2 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J=8.4, 7.2 Hz, 1H), 6.71 (d, J=3.4 Hz, 1H), 6.69 (d, J=1.5 Hz, 1H), 5.65–5.41 (m, 2H), 5.29 (dd, J=7.8, 3.9 Hz, 1H), 4.20 (ddt, J=46.2, 9.5, 6.8 Hz, 2H), 3.56 (dd, J=14.4, 4.5 Hz, 1H), 2.97 (d, J=14.4 Hz, 1H), 2.44 (qd, J=6.7, 1.0 Hz, 2H), 2.31 (s, 1H), 2.02 (qdd, J=7.4, 6.3, 1.2 Hz, 2H), 0.97 (t, J=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (s), 144.0 (s), 134.8 (s), 131.3 (s), 130.9 (s), 124.4 (s), 115.5 (s), 114.6 (s), 70.9 (s), 69.2 (s), 42.4 (s), 32.8 (s), 25.7 (s), 13.7 (s). IR: ν 3327.06, 2961.45, 2925.77, 1604.48, 1583.10, 1465.81, 1260.99, 1139.46, 1046.37, 968.37, 767.96 cm^{-1}. HRMS calcd for $C_{14}H_{18}NaO_2^+$ $[M+Na]^+$: 241.1199, found: 241.1204. Mp (°C): 37–39.

*4.4.15. (Z)-5-(Hex-3-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7u**).* Compound **7u** was obtained in 27% yield as light yellow solid (59.0 mg) from **6u**, R_f=0.2 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.17 (m, 1H), 6.69 (d, J=7.6 Hz, 2H), 5.56–5.37 (m, 2H), 5.30 (s, 1H), 4.19 (ddt, J=48.3, 9.3, 6.9 Hz, 2H), 3.57 (dd, J=14.4, 4.5 Hz, 1H), 2.97 (dd, J=14.4, 0.8 Hz, 1H), 2.50 (q, J=7.0 Hz, 2H), 2.25 (d, J=8.0 Hz, 1H), 2.07 (p, J=7.5 Hz, 2H), 0.97 (t, J=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (s), 144.0 (s), 134.3 (s), 131.3 (s), 130.9 (s), 124.1 (s), 115.5 (s), 114.5 (s), 70.9 (s), 68.9 (s), 42.5 (s), 27.6 (s), 20.7 (s), 14.2 (s). IR: ν 3327.95, 3009.99, 2962.18, 2930.15, 2874.42, 1604.82, 1583.41, 1478.15, 1466.83, 1387.75, 1261.52, 1197.50, 1140.13, 1049.18, 770.12, 730.86 cm^{-1}. HRMS calcd for $C_{14}H_{18}NaO_2^+$ $[M+Na]^+$: 241.11990, found: 241.12040. Mp (°C): 35–37.

*4.4.16. 5-(But-3-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7v**).* Compound **7v** was obtained in 27% yield as light yellow solid (51.3 mg) from **6v**, R_f=0.2 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J=8.4, 7.1 Hz, 1H), 6.71 (dd, J=3.8, 3.1 Hz, 1H), 6.69 (d, J=0.6 Hz, 1H), 5.89 (ddt, J=17.0, 10.3, 6.7 Hz, 1H), 5.28 (d, J=2.6 Hz, 1H), 5.19–5.12 (m, 1H), 5.11–5.05 (m, 1H), 4.25 (ddt, J=50.0, 9.6, 6.7 Hz, 2H), 3.56 (dd, J=14.5, 4.5 Hz, 1H), 2.97 (d, J=14.9 Hz, 1H), 2.57–2.44 (m, 2H), 2.38 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (s), 144.0 (s), 134.5 (s), 131.3 (s), 130.9 (s), 117.0 (s), 115.6 (s), 114.6 (s), 70.9 (s), 68.6 (s), 42.4 (s), 33.9 (s). IR: ν 3297.24, 2954.81, 2920.34, 1604.23, 1584.37, 1478.79, 1467.52, 1391.45, 1265.78, 1139.87, 1102.64, 1053.98, 992.70, 914.94, 773.25 cm^{-1}. HRMS calcd for $C_{12}H_{14}O_2$ [M]: 190.0994, found: 190.0992. Mp (°C): 46–48.

*4.4.17. 5-((2-Methylenedecyl)oxy)bicyclo[4.2.0]octa-1(6),2,4-trien-7-ol (**7w**).* Compound **7w** was obtained in 48% yield as white solid (136.9 mg) from **6w**, R_f=0.4 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J=8.4, 7.2 Hz, 1H), 6.72 (dd, J=15.9,

7.6 Hz, 2H), 5.33–5.20 (m, 1H), 5.12–5.04 (m, 1H), 4.93 (t, *J*=9.9 Hz, 1H), 4.67 (dd, *J*=33.1, 13.0 Hz, 2H), 3.56 (dd, *J*=14.4, 4.6 Hz, 1H), 3.00–2.94 (m, 1H), 2.32 (d, *J*=9.5 Hz, 1H), 2.19–2.04 (m, 2H), 1.56–1.38 (m, 2H), 1.41–1.20 (m, 10H), 0.87 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (s), 145.5 (s), 144.0 (s), 131.3 (s), 131.0 (s), 115.7 (s), 114.7 (s), 111.1 (s), 71.9 (s), 70.8 (s), 42.3 (s), 33.0 (s), 31.9 (s), 29.5 (s), 29.5 (s), 29.3 (s), 27.6 (s), 22.7 (s), 14.2 (s). IR: ν 3326.98, 2925.26, 2854.79, 1604.56, 1584.60, 1474.37, 1260.18, 1197.28, 1139.77, 1097.55, 1045.34, 900.06, 769.66 cm^{-1}. HRMS calcd for $C_{19}H_{28}NaO_2^+$ $[M+Na]^+$: 311.1982, found: 311.1982. Mp (°C): 39–40.

4.5. General procedure D: [2+2] coupling II

To a 100 mL flamed-dried flask equipped with stir bar and a nitrogen-filled balloon was added THF (20 mL). The system was cooled to 0 °C with an ice-water bath before *n*-BuLi (2.5 M in hexane, 6 mmol, 1.5 equiv) was added dropwise. Upon completion, the system was warmed to rt and stirred for 16 h under nitrogen atmosphere. At the same time, to a 30 mL flamed-dried flask equipped with a stir bar and a nitrogen-filled balloon were added 2,2,6,6-tetramethylpiperidine (4.8 mmol, 1.2 equiv) and THF (12 mL). After cooled to 0 °C with an ice-water bath, *n*-BuLi (2.5 M in hexane, 4.8 mmol, 1.2 equiv) was added dropwise and the reaction was stirred at 0 °C for 0.5 h. The previous 100 mL flask was cooled to −78 °C with an acetone-dry ice bath and benzyne precursor (4 mmol, 1 equiv) in THF (5 mL) was added before in situ generated lithium tetramethylpiperidine was added dropwise. The reaction was stirred at −78 °C for 3h and was warmed to rt before quenching by adding aqueous NH_4Cl (30 mL). The mixture was extracted with ethyl acetate (30 mL×3), washed with brine, and dried with Na_2SO_4. The combined organic extract was concentrated under reduced pressure and purified by column chromatography on silica gel to afford the following compounds.

*4.5.1. 5-(Benzyloxy)-2-chlorobicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7h**).* Compound **7h** was obtained in 39% yield as a white solid (202 mg) from **6h**, R_f=0.2 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5H), 7.14 (d, *J*=8.9 Hz, 1H), 6.77 (d, *J*=8.9 Hz, 1H), 5.33 (d, *J*=12.2 Hz, 1H), 5.23 (d, *J*=12.2 Hz, 1H), 5.15 (dd, *J*=8.7, 3.7 Hz, 1H), 3.55 (dd, *J*=14.7, 4.5 Hz, 1H), 2.98 (d, *J*=14.8 Hz, 1H), 2.25 (d, *J*=9.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5 (s), 140.7 (s), 137.1 (s), 132.0 (s), 130.9 (s), 128.6 (s), 128.0 (s), 127.1 (s), 119.7 (s), 117.2 (s), 71.4 (s), 69.8 (s), 41.0 (s). IR: ν 3243, 2917, 2360, 2343, 1579, 1467, 1455, 1262, 1187, 1105, 1067, 996, 913, 826, 696 cm^{-1}. HRMS calcd for $C_{15}H_{13}ClNaO_2^+$ $[M+Na]^+$: 283.0496, found: 283.0497. Mp (°C): 85–88.

*4.5.2. 5-(Dimethylamino)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (**7i**).* Compound **7i** was obtained as an orange oil from **6i** in 15% (101 mg) and **6j** in 16% (118 mg), R_f=0.15 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J*=8.5, 7.1 Hz, 1H), 6.46 (d, *J*=7.1 Hz, 1H), 6.41 (d, *J*=8.5 Hz, 1H), 5.28 (ddd, *J*=10.6, 4.4, 1.5 Hz, 1H), 3.53 (dd, *J*=14.2, 4.4 Hz, 1H), 3.01 (s, 6H), 2.93–2.86 (m, 1H), 2.07 (d, *J*=10.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3 (s), 143.8 (s), 131.1 (s), 130.6 (s), 111.4 (s), 110.4 (s), 71.9 (s), 42.0 (s), 40.3 (s). IR: ν 2109, 1640, 1501, 1439, 1355, 1230, 1041, 994, 696 cm^{-1}. HRMS calcd for $C_{10}H_{13}NNaO^+$ $[M+Na]^+$: 186.0895, found: 186.0892.

4.6. General procedure E: [2+2] coupling III

To a 30 mL flamed-dried flask equipped with stir bar and a nitrogen-filled balloon were added 2,2,6,6-tetramethylpiperidine (1.2 equiv) and THF (12 mL). After cooled to 0 °C with an ice-water bath, *n*-BuLi (2.5 M in hexane, 1.2 equiv) was added dropwise and the reaction was stirred at 0 °C for 0.5 h. To a 100 mL flame-dried flask equipped with a stir bar and a nitrogen-filled balloon were added THF (30 mL), benzyne precursor (1 equiv), and corresponding ketene silyl acetals[9] (1.5 equiv) and was cooled to −78 °C with an acetone-dry ice bath before in situ generated lithium tetramethylpiperidine was added dropwise. The reaction was monitored and aqueous NH_4Cl was added upon disappearance of the benzyne precursor. After warming to rt, the reaction mixture was extracted with ethyl acetate (30 mL×3), washed with brine, and concentrated under reduced pressure. Acetonitrile (30 mL) was added to the concentrated reaction system and cooled to 0 °C with an ice-water bath followed by slow addition of hydrofluoric acid (27.6 M, 10 equiv). Upon completion, the reaction was heated to 40 °C overnight before water (100 mL) was added. The mixture was extracted with ethyl acetate (30 mL×3), washed with brine, and dried with Na_2SO_4. The combined organic extract was concentrated under reduced pressure and purified by column chromatography on silica gel to afford the following compounds.

*4.6.1. 5-(Benzyloxy)-8-methylbicyclo[4.2.0]octa-1,3,5-trien-7-one (**9**).* Compound **9** was obtained as light yellow oil (271 mg) from **6d** and *tert*-butyl((1-methoxyprop-1-en-1-yl)oxy)dimethylsilane in 23% yield, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.30 (m, 6H), 7.02 (d, *J*=7.0 Hz, 1H), 6.89 (d, *J*=8.4 Hz, 1H), 5.45 (s, 2H), 4.21 (q, *J*=7.2 Hz, 1H), 1.47 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3 (s), 157.0 (s), 152.6 (s), 137.8 (s), 136.4 (s), 130.7 (s), 128.5 (s), 128.2 (s), 127.9 (s), 116.7 (s), 114.2 (s), 74.0 (s), 58.3 (s), 15.0 (s). IR: ν 2964, 2927, 2360, 2342, 1756, 1602, 1571, 1473, 1452, 1386, 1273, 1161, 1125, 991, 886, 795, 767, 748, 699 cm^{-1}. HRMS calcd for $C_{16}H_{14}NaO_2^+$ $[M+Na]^+$: 261.0886, found: 261.0879.

*4.6.2. 8-Ethyl-5-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**10**).* Compound **10** was obtained as colorless oil (876 mg) from **6a** and *tert*-butyl((1-methoxybut-1-en-1-yl)oxy)dimethylsilane in 62% yield, R_f=0.8 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J*=8.4, 7.1 Hz, 1H), 6.99 (d, *J*=7.1 Hz, 1H), 6.78 (d, *J*=8.4 Hz, 1H), 4.13–4.06 (m, 4H), 1.98–1.72 (m, 2H), 1.04 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.9 (s), 156.0 (s), 153.5 (s), 137.5 (s), 131.1 (s), 116.0 (s), 114.6 (s), 65.0 (s), 59.7 (s), 23.3 (s), 11.5 (s). IR: ν 2963, 2934, 2876, 2359, 2340, 1766, 1602, 1574, 1482, 1455, 1435, 1277, 1157, 1123, 1020, 941, 799 cm^{-1}. HRMS calcd for $C_{16}H_{14}NaO_2^+$ $[M+Na]^+$: 261.0886, found: 261.0879.

4.7. General procedure F: DMP oxidation I

A 10 mL flask equipped with a stir bar was charged with benzocyclobutenols (0.2 mmol, 1 equiv) and DMP (0.3 mmol, 1.5 equiv). DCM (2 mL) was added and the reaction was monitored by TLC. Upon disappearance of benzocyclobutenols, the reaction was directly purified by column chromatography on silica gel to afford the following compounds.

*4.7.1. 5-Methoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**8a**).* Compound **8a**[12] (CAS No.: 66947-60-2) was obtained in 98% yield as a white solid (45 mg) from **7a**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 1H), 7.02 (d, *J*=7.0 Hz, 1H), 6.79 (d, *J*=8.4 Hz, 1H), 4.12–4.09 (m, 3H), 3.91 (d, *J*=0.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (s), 153.4 (s), 150.6 (s), 137.6 (s), 132.3 (s), 115.8 (s), 115.1 (s), 59.8 (s), 51.3 (s).

*4.7.2. 5-(Benzyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8c**).* Compound **8c**[8c] (CAS No.: 169615-68-3) was obtained in 96% yield as a white solid (44 mg) from **7c**, R_f=0.4 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.31 (m, 6H), 7.05

(dd, *J*=7.1, 0.5 Hz, 1H), 6.89 (dd, *J*=8.4, 0.5 Hz, 1H), 5.47 (s, 2H), 3.94 (s, 2H).

*4.7.3. 4,5-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**8e**).* Compound **8e**[12] (CAS No.: 81447-58-7) was obtained in 88% yield as a white solid (46 mg) from **7e**, R_f=0.25 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J*=7.7 Hz, 1H), 6.90 (dt, *J*=7.6, 0.9 Hz, 1H), 4.16 (s, 3H), 3.83 (s, 3H), 3.82 (d, *J*=0.9 Hz, 2H).

*4.7.4. 2,5-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**8f**).* Compound **8f**[10j] (CAS No.: 75833-45-3) was obtained in 95% yield as a white solid (51 mg) from **7f**, R_f=0.5 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J*=8.9 Hz, 1H), 6.73 (dt, *J*=9.0, 0.8 Hz, 1H), 4.04 (s, 3H), 4.02 (d, *J*=0.8 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6 (s), 148.4 (s), 147.6 (s), 133.3 (s), 132.2 (s), 124.4 (s), 117.6 (s), 59.7 (s), 56.8 (s), 50.6 (s). HRMS calcd for $C_{10}H_{10}NaO_3^+$ $[M+Na]^+$: 201.0522, found: 201.0519. Mp (°C): 92–95.

*4.7.5. 5-(Benzyloxy)-2-chlorobicyclo[4.2.0]octa-1,3,5-trien-7-one (**8h**).* Compound **8h** was obtained in 98% yield as a light yellow solid (82 mg) from **7h**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (m, 6H), 6.86 (d, *J*=8.8 Hz, 1H), 5.42 (s, 2H), 3.96 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.7 (s), 151.1 (s), 147.3 (s), 137.6 (s), 136.0 (s), 133.3 (s), 128.6 (s), 128.3 (s), 127.9 (s), 119.9 (s), 119.1 (s), 74.4 (s), 50.7 (s). IR: ν 2360, 2340, 1755, 1597, 1565, 1479, 1454, 1393, 1276, 1259, 1110, 977, 918, 838, 756, 717, 694, 668, 652 cm^{-1}. HRMS calcd for $C_{15}H_{11}ClNaO_2^+$ $[M+Na]^+$: 281.0340, found: 281.0342. Mp (°C): 115–117.

*4.7.6. 5-((2-Methylallyl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8l**).* Compound **8l**[6a] (CAS No.: 1402160-41-1) was obtained in 98% yield as a colorless oil (56 mg) from **7l**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J*=8.4, 7.1 Hz, 1H), 7.01 (d, *J*=6.5 Hz, 1H), 6.85 (d, *J*=8.4 Hz, 1H), 5.09–5.03 (m, 1H), 4.98–4.92 (m, 1H), 4.83 (s, 2H), 3.90 (s, 2H), 1.83 (s, 3H).

*4.7.7. (E)-5-(But-2-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8m**).* Compound **8m** was obtained in 94% yield as a light yellow solid (54 mg) from **7m**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J*=8.4, 7.1 Hz, 1H), 7.01 (dd, *J*=7.1, 0.5 Hz, 1H), 6.81 (dd, *J*=8.4, 0.5 Hz, 1H), 5.90 (dqt, *J*=15.2, 6.4, 1.2 Hz, 1H), 5.71 (dtq, *J*=15.8, 6.3, 1.6 Hz, 1H), 4.86–4.82 (m, 2H), 3.91 (s, 2H), 1.74 (ddd, *J*=6.5, 2.6, 1.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (s), 152.2 (s), 150.5 (s), 137.7 (s), 132.3 (s), 131.4 (s), 125.5 (s), 116.3 (s), 114.9 (s), 72.8 (s), 51.1 (s), 17.9 (s). IR: ν 1758, 1610, 1573, 1472, 1455, 1381, 1264, 1158, 1118, 1050, 966, 751, 668 cm^{-1}. HRMS calcd for $C_{12}H_{12}NaO_2^+$ $[M+Na]^+$: 211.0730, found: 211.0725. Mp (°C): 41–43.

*4.7.8. 5-((3-Methylbut-2-en-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8n**).* Compound **8n** was obtained in 77% yield as a colorless oil (46 mg) from **7n**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J*=8.4, 7.1 Hz, 1H), 6.99 (dd, *J*=7.1, 0.6 Hz, 1H), 6.79 (dd, *J*=8.4, 0.6 Hz, 1H), 5.49 (tdt, *J*=7.0, 2.8, 1.4 Hz, 1H), 4.87 (d, *J*=7.0 Hz, 2H), 3.89 (t, *J*=0.8 Hz, 2H), 1.77 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0 (s), 152.4 (s), 150.5 (s), 139.5 (s), 137.6 (s), 132.4 (s), 119.0 (s), 116.3 (s), 114.9 (s), 69.1 (s), 51.1 (s), 25.8 (s), 18.3 (s). IR: ν 2918, 1772, 1678, 1601, 1583, 1476, 1389, 1352, 1281, 1253, 1132, 1130, 1052, 973, 945, 783, 754, 673, 577 cm^{-1}. HRMS calcd for $C_{13}H_{14}NaO_2^+$ $[M+Na]^+$: 225.0891, found: 225.0883.

*4.7.9. 5-((3-Methylbut-3-en-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8o**).* Compound **8o**[6a] (CAS No.: 1402160-46-6) was obtained in 98% yield as a colorless oil (60 mg) from **7o**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J*=8.4, 7.1 Hz, 1H), 6.98 (dd, *J*=7.1, 0.6 Hz, 1H), 6.78 (dd, *J*=8.4, 0.6 Hz, 1H), 4.84–4.78 (m, 2H), 4.48 (t, *J*=6.7 Hz, 2H), 3.89 (s, 2H), 2.47 (t, *J*=6.7 Hz, 2H), 1.79 (s, 3H).

*4.7.10. 5-(Hex-3-yn-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8p**).* Compound **8p**[7] was obtained in 93% yield as a colorless oil (40 mg) from **7p**, R_f=0.4 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J*=8.4, 7.1 Hz, 1H), 7.11–6.94 (m, 1H), 6.84 (dd, *J*=8.4, 0.4 Hz, 1H), 4.45 (t, *J*=6.6 Hz, 1H), 3.90 (s, 1H), 2.63 (t, *J*=6.6, 2.4 Hz, 1H), 2.15 (qt, *J*=7.5, 2.4 Hz, 1H), 1.10 (t, *J*=7.5 Hz, 1H).

*4.7.11. 5-((5-Phenylpent-4-yn-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8q**).* Compound **8q**[7] was obtained in 86% yield as a light yellow oil (48 mg) from **7q**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.36 (m, 3H), 7.29–7.23 (m, 3H), 7.00 (dd, *J*=7.1, 0.6 Hz, 1H), 6.81 (dd, *J*=8.4, 0.5 Hz, 1H), 4.53 (t, *J*=6.0 Hz, 2H), 3.89 (s, 2H), 2.61 (t, *J*=7.1 Hz, 2H), 2.11–2.04 (m, 2H).

*4.7.12. 5-(Allyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8r**).* Compound **8r**[6a] (CAS No.: 1402160-48-8) was obtained in 74% yield as colorless oil (21.9 mg) from **7r**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J*=8.4, 7.1 Hz, 1H), 7.01 (d, *J*=7.1 Hz, 1H), 6.83 (dd, *J*=8.4, 0.5 Hz, 1H), 6.03 (ddt, *J*=17.2, 10.6, 5.3 Hz, 1H), 5.40 (dq, *J*=17.3, 1.6 Hz, 1H), 5.25 (dq, *J*=10.5, 1.4 Hz, 1H), 4.90 (dt, *J*=5.4, 1.5 Hz, 1H), 3.90 (s, 1H).

*4.7.13. (E)-5-((2-Phenylbut-2-en-1-yl)oxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8s**).* Compound **8s** was obtained in 93% yield as colorless oil (24.6 mg) from **7s**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 6H), 6.98 (dd, *J*=7.1, 0.4 Hz, 1H), 6.77 (dd, *J*=8.4, 0.5 Hz, 1H), 5.99 (qd, *J*=6.9, 6.0 Hz, 1H), 5.09 (s, 2H), 3.89 (s, 2H), 1.66 (dt, *J*=7.0, 1.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0 (s), 152.3 (s), 150.4 (s), 138.1 (s), 137.6 (s), 136.7 (s), 132.4 (s), 128.8 (s), 128.1 (s), 127.4 (s), 127.0 (s), 116.5 (s), 115.0 (s), 77.1 (s), 51.1 (s), 14.7 (s). IR: ν 3056.04, 2917.02, 1760.50, 1600.41, 1571.43, 1471.32, 1270.01, 1158.39, 1127.93, 1047.97, 975.00, 780.92, 701.08 cm^{-1}. HRMS calcd for $C_{18}H_{16}NaO_2^+$ $[M+Na]^+$: 287.1043, found: 287.1033.

*4.7.14. (E)-5-(Hex-3-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8t**).* Compound **8t** was obtained in 94% yield as colorless oil (20.3 mg) from **7t**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J*=8.4, 7.1 Hz, 1H), 6.98 (dd, *J*=7.1, 0.5 Hz, 1H), 6.79 (dd, *J*=8.5, 0.5 Hz, 1H), 5.75–5.37 (m, 2H), 4.38 (t, *J*=6.7 Hz, 2H), 3.89 (s, 2H), 2.48–2.41 (m, 2H), 2.06–1.96 (m, 2H), 0.95 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0 (s), 152.6 (s), 150.5 (s), 137.6 (s), 134.9 (s), 132.3 (s), 124.2 (s), 116.2 (s), 114.8 (s), 72.1 (s), 51.1 (s), 32.5 (s), 25.6 (s), 13.7 (s). IR: ν 2962.01, 2930.58, 2359.68, 2340.51, 1770.32, 1604.37, 1572.65, 1476.29, 1460.12, 1275.54, 1158.85, 1128.56, 1052.18, 967.48, 782.60 cm^{-1}. HRMS calcd for $C_{14}H_{16}NaO_2^+$ $[M+Na]^+$: 239.1043, found: 239.1059.

*4.7.15. (Z)-5-(Hex-3-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8u**).* Compound **8u** was obtained in 97% yield as colorless oil (21.0 mg) from **7u**, R_f=0.6 (Hexane/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J*=8.4, 7.1 Hz, 1H), 6.99 (dd, *J*=7.1, 0.5 Hz, 1H), 6.78 (dd, *J*=8.4, 0.5 Hz, 1H), 6.78 (dd, *J*=8.4, 0.5 Hz, 1H), 5.55–5.38 (m, 1H), 4.37 (t, *J*=6.6 Hz, 1H), 3.89 (s, 1H), 2.54–2.47 (m, 1H), 2.10–2.01 (m, 1H), 0.96 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (s), 152.6 (s), 150.5 (s), 137.6 (s), 134.4 (s), 132.2 (s), 124.0 (s), 116.2 (s), 114.8 (s), 71.9 (s), 51.1 (s), 27.3 (s), 20.7 (s), 14.2 (s). IR: ν 2962.50, 2359.54, 1768.41, 1603.24, 1573.12, 1476.17, 1459.91, 1390.98,

1352.44, 1275.96, 1158.73, 1127.91, 1051.66, 782.46 cm^{-1}. HRMS calcd for $C_{14}H_{16}NaO_2^+$ $[M+Na]^+$: 239.1043, found: 239.1050.

*4.7.16. 5-(But-3-en-1-yloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8v**).* Compound **8v**[6b] (CAS No.: 1415357-68-4) was obtained in 92% yield as colorless oil (17.3 mg) from **7v**, R_f=0.6 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J=8.4, 7.1 Hz, 1H), 6.99 (dd, J=7.1, 0.5 Hz, 1H), 6.79 (dd, J=8.4, 0.5 Hz, 1H), 5.89 (ddt, J=17.0, 10.3, 6.7 Hz, 1H), 5.15 (ddd, J=17.2, 3.4, 1.6 Hz, 1H), 5.11–5.06 (m, 1H), 4.43 (t, J=6.5 Hz, 2H), 3.89 (s, 2H), 2.52 (qt, J=6.6, 1.4 Hz, 2H).

*4.7.17. 5-((2-Methylenedecyl)oxy)bicyclo[4.2.0]octa-1(6),2,4-trien-7-one (**8w**).* Compound **8w** was obtained in 86% yield as colorless oil (37.2 mg) from **7w**, R_f=0.75 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J=8.4, 7.1 Hz, 1H), 7.00 (dd, J=7.0, 0.4 Hz, 1H), 6.83 (dd, J=8.4, 0.5 Hz, 1H), 5.11–5.05 (m, 1H), 4.97–4.91 (m, 1H), 4.84 (s, 2H), 3.89 (s, 2H), 2.20–2.05 (m, 2H), 1.52–1.39 (m, 2H), 1.37–1.18 (m, 10H), 0.86 (t, J=6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (s), 152.4 (s), 150.5 (s), 144.6 (s), 137.7 (s), 132.4 (s), 116.3 (s), 115.1 (s), 111.8 (s), 74.7 (s), 51.2 (s), 33.0 (s), 31.9 (s), 29.5 (s), 29.4 (s), 29.3 (s), 27.5 (s), 22.7 (s), 14.1 (s). IR: ν 2926.05, 2854.75, 1768.76, 1603.38, 1574.27, 1474.60, 1275.33, 1158.42, 1128.28, 1050.87, 990.80, 946.75, 898.03, 782.03, 758.76 cm^{-1}. HRMS calcd for $C_{19}H_{26}NaO_2^+$ $[M+Na]^+$: 309.1825, found: 309.1824.

4.8. General procedure G: DMP oxidation II

A 10 mL flask equipped with a stir bar was charged with benzocyclobutenols (0.2 mmol, 1 equiv), DMP (0.3 mmol, 1.5 equiv), and $NaHCO_3$ (0.3 mmol, 1.5 equiv). DCM (2 mL) was added and the reaction was monitored by TLC. Upon disappearance of benzocyclobutenols, the reaction was directly purified by column chromatography on silica gel to afford the following compounds.

*4.8.1. 5-(2-((tert-Butyldimethylsilyl)oxy)ethoxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8g**).* Compound **8g** was obtained in 85% yield as a white solid (40 mg) from **7g**, R_f=0.7 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J=8.4, 7.1 Hz, 1H), 6.99 (dd, J=7.1, 0.4 Hz, 1H), 6.82 (dd, J=8.4, 0.4 Hz, 1H), 4.47–4.44 (m, 2H), 3.96–3.93 (m, 2H), 3.89 (s, 2H), 0.86 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0 (s), 152.7 (s), 150.4 (s), 137.7 (s), 132.3 (s), 116.3 (s), 114.9 (s), 73.8 (s), 62.1 (s), 51.1 (s), 25.9 (s), 18.4 (s), −5.2 (s). IR: ν 2955, 2927, 2857, 1766, 1604, 1574, 1471, 1442, 1277, 1253, 1137, 1124, 1092, 1060, 955, 946, 881, 833, 787 cm^{-1}. HRMS calcd for $C_{16}H_{24}NaO_3Si^+$ $[M+Na]^+$: 315.1387, found: 315.1390. Mp (°C): 46–48.

*4.8.2. 5-(Dimethylamino)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**8i**).* Compound **8i** was obtained in 21% yield as an orange oil (7 mg) from **7i**, R_f=0.3 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J=8.6, 6.9 Hz, 1H), 6.64 (d, J=6.9 Hz, 1H), 6.36 (d, J=8.6 Hz, 1H), 3.76 (s, 2H), 3.18 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.8 (s), 151.3 (s), 145.1 (s), 137.2 (s), 129.6 (s), 110.3 (s), 109.0 (s), 49.7 (s), 40.8 (s). IR: ν 2919, 1734, 1616, 1576, 1506, 1436, 1418, 1383, 1191, 1116, 1046, 89, 766, 643 cm^{-1}. HRMS calcd for $C_{10}H_{12}NO^+$ $[M+H]^+$: 162.0913, found: 162.0907.

4.9. Gram-scale synthesis of compound 3

To a 1000 mL flamed-dried flask equipped with a stir bar and a nitrogen-filled balloon was added THF (250 mL). The system was cooled to 0 °C with an ice-water bath before *n*-BuLi (2.5 M in hexane, 77.6 mL, 194 mmol, 1.7 equiv) was added dropwisely. Upon completion, the system was warmed to rt and stirred for 16 h under nitrogen atmosphere. At the same time, to a 250 mL flamed-dried flask equipped with a stir bar and a nitrogen-filled balloon were added 2,2,6,6-tetramethylpiperidine (24.16 g, 171 mmol, 28.86 mL, 1.5 equiv) and THF (120 mL). After cooled to 0 °C with an ice-water bath, *n*-BuLi (2.5 M in hexane, 68.4 mL, 171 mmol, 1.5 equiv) was added dropwisely and the reaction was stirred at 0 °C for 0.5 h. The previous 1000 mL flask was cooled to −78 °C with an acetone-dry ice bath and **6d** (30 g, 114 mmol, 1 equiv) in THF (120 mL) was added before in situ generated lithium tetramethylpiperidine was added dropwisely. The reaction was stirred at −78 °C for 0.5 h and was quenched by adding aqueous NH_4Cl. The mixture was then warmed to rt and H_2O (200 mL) was added. The mixture was extracted with ethyl acetate (200 mL×3), washed with brine, and dried with Na_2SO_4. The combined organic extract was concentrated under reduced pressure and used directly without purification.

To a 1000 mL flamed-dried flasks equipped with a stir bar and a nitrogen-filled balloon was added oxalyl chloride (21.84 g, 172 mmol, 1.5 equiv) and DCM (200 mL). The flask was cooled to −78 °C and DMSO (26.9 g, 344 mmol, 3 equiv) in DCM (150 mL) was added dropwise. After the reaction was stirred at −78 °C for 20 min, **7c** (from previous step) in DCM (150 mL) was added dropwisely and the system was stirred at −78 °C for another 1 h. Triethylamine (69.7 g, 689 mmol, 6 equiv) was added slowly. The reaction was then warmed to rt followed by quenched with H_2O (100 mL) and extracted with ethyl acetate (150 mL×3). The combined organic extract was washed with brine and dried over Na_2SO_4. The organic extract was concentrated under reduced pressure and purified by column chromatography on silica gel to give 24.5 g of crude **8c**.

A 1000 mL flask equipped with a stir bar was charged with crude **8c** (from previous step), $Pd(OH)_2$ (5.4 g, Pd 20% on carbon, nominally 50% water, Pearlman's catalyst), HOAc (400 mL), and 6 M HCl (80 mL). The system was quickly put under vacuum and back-filled with H_2 gas for three times. The flask was then equipped with a H_2-filled balloon and stirred at 40 °C for overnight. The black reaction mixture was directly filtered through Celite, and the filtrate was concentrated directly under rotavapor. The residue was purified by column chromatography on silica gel to give 11.5 g of compound **3** as a light yellow solid in 75% yield over three steps.

*4.9.1. 5-Hydroxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**3**[6a]).* R_f=0.2 (Hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.45 (dd, J=8.4, 7.1 Hz, 1H), 7.02 (dd, J=7.1, 0.5 Hz, 1H), 6.81 (dd, J=8.4, 0.5 Hz, 1H), 3.91 (t, J=0.7 Hz, 1H).

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Supplementary data

NMR spectra of all new compounds are found in Supplementary data. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.080.

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