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Halocycloalkenones as Diels–Alder Dienophiles. Applications to Generating Useful Structural Patterns

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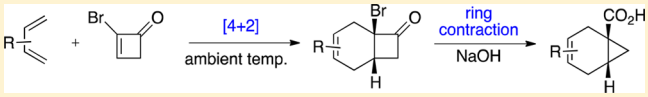
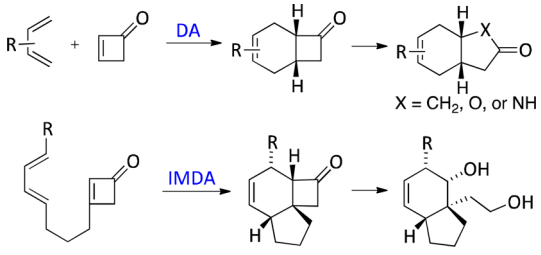
Supporting Information

ABSTRACT: Halocycloalkenones are demonstrated to function as potent dienophiles in inter- and intramolecular Diels–Alder cycloadditions. We have found 2-brominated cycloalkenone dienophiles to be both highly *endo* selective and significantly more reactive than their nonhalogenated parent compounds. A method for the facile conversion of brominated cyclobutanone DA adducts to synthetically useful cyclopropyl functional handles is described.



Recently, we have been investigating [4 + 2] cycloaddition reactions of cyclobutenones.[1] In our first foray, we examined unsubstituted cyclobutenone as a dienophile in the intermolecular Diels–Alder (DA) reaction. This substrate was shown to be far more reactive, both under strictly thermal and under Lewis acid–mediated conditions, than the "homologous," and rather more classical dienophiles, cyclopentenone and cyclohexenone. We went on to show that unsubstituted cyclobutenones could be used as precursors of formal cycloadducts of larger dienophiles, which are in themselves rather sluggish in their propensity for cycloaddition reactions (Scheme 1).

Scheme 1. Inter- and Intramolecular [4 + 2] Cycloaddition Reactions of Cyclobutenones



We have also described the results of another arm of the study wherein we investigated intramolecular Diels–Alder (IMDA) reactions of the 3-substituted cyclobutenones.[2] It was found that, with a three-carbon tether separating the diene and the 3-substituted cyclobutenone, highly *endo*-selective IMDA reaction occurs, giving rise to a tricyclic system bearing a *trans*-fused hydrindene motif. Chemoselective cleavage of the adduct's four-membered ring serves to expose the *trans*-hydrindene, with diverse functionality at the junction and well-controlled stereochemical biases in the six-membered ring. Furthermore, the double bond placement within the six-membered ring corresponds to a site that is otherwise inaccessible via a direct DA construction.

Both of these efforts were pursued as part of an overarching interest in learning how to create structural patterns that are not readily available by the currently understood protocols of classical organic synthesis. The ability to gain ready access to such diverse structures serves to enhance the applicability of a strategy for complex synthesis, which we have termed pattern recognition analysis (PRA).[3] Unlike the more traditional, and certainly more general, intellectual construct of retrosynthesis by prioritized strategic bond disconnection (PSBD),[4] PRA operates by seeking to identify established subunits and using these as core elements in retrosynthesis design. Having identified a synthetically accessible core motif, which contains suitable levels of functionality, one tries to proceed to the target by enhancing or attenuating molecular complexity. The usefulness of PRA is directly related to the accessibility of diverse structural patterns.

The research described in this paper started by asking whether the synthetic value of the "cyclobutenone" concept could be enhanced by incorporating additional functionality on the ring. We were posing three questions. First, what will be the consequences of the additional functionality on the quality of the DA reaction? Moreover, could such compounds be readily synthesized? Finally, could the products of such DA reactions be exploited in building potentially useful structures to expand the reach of PRA?

We began by wondering about the consequences of placing a bromine atom on the vinylic α-carbon (i.e., C2) of the cyclobutenone. Happily, we could prepare the compound in a remarkably straightforward fashion from cyclobutenone (**1**), whose synthesis in significant gram quantities has recently been

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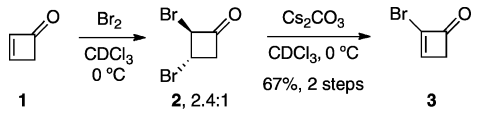
described.[5] As shown in Scheme 2, treatment of compound **1** with bromine[6] gives rise to the dibromo compound **2** as a 2.4:1

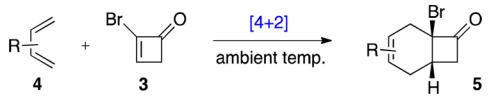
Scheme 2. Synthesis of 2-Bromocyclobutenone (3)

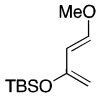
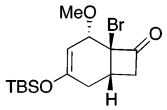
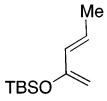
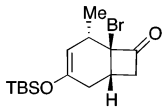
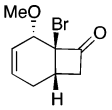
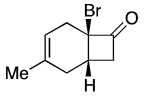
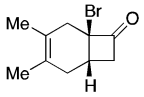
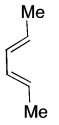
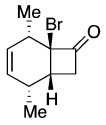
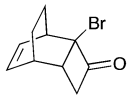


trans/*cis* mixture. Reaction of **2** with excess cesium carbonate gives rise to 2-bromocyclobutenone (**3**).

We first inquired as to the dienophilic capacities of compound **3**. As demonstrated in Table 1, our studies showed

Table 1. Diels-Alder Cycloadditions with Dienophile 3

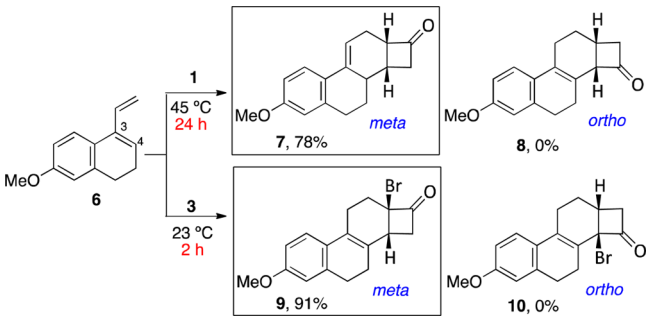


Entry	Diene		Product		Yield, Time
1		**4a**		**5a**	92%, 3 h
2		**4b**		**5b**	88%, 6 h
3		**4c**		**5c**	94%, 3 h
4		**4d**		**5d**	86%, 20 h
5		**4e**		**5e**	92%, 18 h
6		**4f**		**5f**	97%, 18 h
7		**4g**		**5g**	90%, 24 h

3 to be a more reactive dienophile than is the des-halo compound **1**. Fascinatingly, all of the DA reactions occurred at ambient temperature and produced DA adducts as single diastereomers. While activated dienes encouraged rapid reaction times (entries 1–3), it is important to note that, in contrast to the parent cyclobutenone, relatively unreactive hydrocarbon dienes (entries 4–7) also participated in high-yielding cycloaddition without the aid of Lewis acid catalysis.

Subsequently, our attention turned to the study of Dane's diene, **6**. Previously, we had discovered that under thermal (or careful Lewis acid catalyzed) settings, cyclobutenone itself reacts with Dane's diene to provide **7**, as a single *meta* regioisomer, in 78% yield. The cycloaddition with **3** was more facile, providing cycloadduct **9**, as a single regioisomer in 91% yield (Scheme 3). These results are instructional for several

Scheme 3. Diels–Alder Reactions of Dane's Diene (6) with Dienophiles 1 and 3



reasons. Traditionally, the DA chemistry of Dane's diene has not been straightforward.[7] Generally, thermally activated DA reactions with Dane's diene favor *ortho* orientation; while Lewis acid catalysis favors *meta* orientation.[8] In sharp contrast, with cyclobutenone-based dienophiles **1** and **3**, DA reactions give only the *meta* product under both thermal *and* Lewis acid catalyzed conditions. We hypothesize that because these particular dienophiles are exceptionally electrophilic "Michael–type" DA acceptors, they have greater asynchronicity in a DA transition state, perhaps approaching, in the extreme, a formal stepwise process. The cyclobutenone may be sufficiently self-activated to approximate the effects of catalysis on other more traditional dienophiles, both in terms of *endo* and *meta* selectivity. Furthermore, the product observed from reaction with 2-bromocyclobutenone featured complete olefin migration.[9] Thus, following standard steroid numbering, the initial $\Delta^{9(11)}$ cyclohexene double bond isomerized to $\Delta^{8(9)}$, connecting the *B* and *C* rings through a tetrasubstituted olefin.

Based on data from our previous studies directed to the *trans*-DA paradigm,[10] we had observed that α-halogenation tended to enhance the dienophilicity of cyclopentenone and cyclohexenone dienophiles.[11] This reactivity order was confirmed by performing a set of competition experiments. Under thermal conditions (Table 2, entries 1 and 2), the 2-halocycloalkenones, **12** and **17**, completely dominate the course of the DA reaction with 2,3-dimethyl-1,3-butadiene (**13**), providing adducts **15** and **19** in 55% and 69% yield, respectively. Not surprisingly, under thermal settings, 2-bromocyclobutenone **3** vastly outperformed the parent cyclobutenone **1**, which does require Lewis acid catalysis to react with relatively marginally activated dienes (entry 3). This trend in reactivity was also observed under Lewis acid catalysis (entry 4), as 1-bromocyclohexenone **12** was the major dienophilic partner, providing products **14** and **15** in ca. 1:17 ratio. While at first glance, one might have thought that the steric effect of the halogen at the reaction site could have deactivated the dienophile, apparently the electronic characteristics of the bromine significantly override hindrance issues.

With a pool of angularly brominated DA adducts at hand, we next hoped to utilize this system to generate compounds corresponding to formal DA adducts, yet arising from the reaction of nonexistent or unattainable dienophiles, such as **22**. For example, when treated with sodium hydroxide, compounds **9**, **5d**, and **5e** easily undergo a quasi-Favorskii ring contraction to provide the corresponding cyclopropane acids **21a–c** (Table

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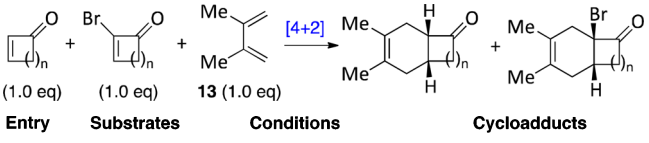
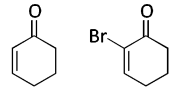
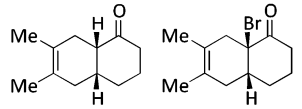
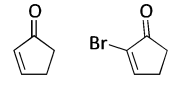
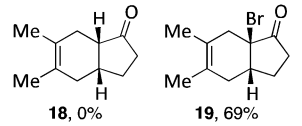
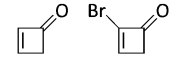
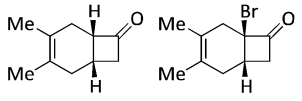
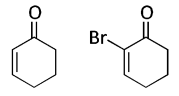
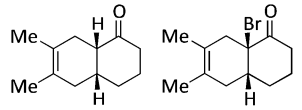
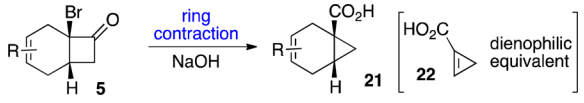
Table 2. Competition Study: Effect of α-Halogenation on Dienophile Reactivity

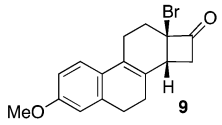
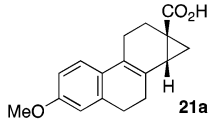
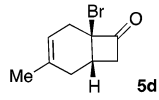
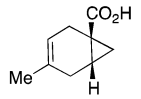
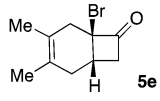
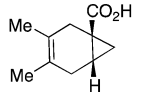
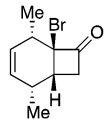
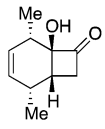


Entry	Substrates	Conditions	Cycloadducts
1	 11 12	toluene 120 °C, 12 h	 14, 0% 15, 55%
2	 16 17	toluene 120 °C, 12 h	 18, 0% 19, 69%
3	 1 3	$CDCl_3$ 23 °C, 12 h	 20, 0% 5e, 70%
4	 11 12	10% $MeAlCl_2$ CH_2Cl_2, 2 h	 14, 5% 15, 87%

3, entries 1−3).[12] Amazingly, this process occurs with a reaction time of just five minutes, likely proceeding through a

Table 3. Functionalization of DA Adducts: Access to Cyclopropane Motifs

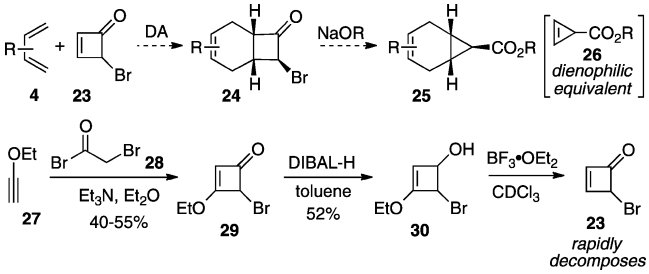


Entry	Cycloadduct	Product	Yield
1	 9	 21a	80%
2	 5d	 21b	67%
3	 5e	 21c	72%
4	 5f	 21d	56%

semibenzilic mechanism. Interestingly, compound **5f** proceeded to give the α-hydroxy ketone **21d** with net replacement of the bromide with hydroxide (entry 4). The mechanism of this transformation awaits clarification.[13]

We next attempted to interrogate the dienophilicity of the 4-bromo compound **23**. DA cycloaddition with generic diene **4** would generate a compound, such as **24**, that is brominated at the methylene group of the resulting cycloadduct (Scheme 4).

Scheme 4. Attempted Synthesis of 4-Bromocyclobutenone (23)



Following exposure to base, ring contraction would provide compounds of the type **25**, which is formally the product of a DA cycloaddition with the cyclopropene acid **26**.[14] In the forward direction, monobromoketene[15] was generated in situ and underwent [2 + 2] cycloaddition with ethoxyacetylene **27** to provide the strained vinylogous ester **29**.[16] Following some early setbacks, it was found that DIBAL-H cleanly reduces the ketone to allylic alcohol **30**, which could be unraveled in the presence of a small amount of BF_3 etherate to furnish 4-bromocyclobutenone **23** as a solution in $CDCl_3$. Unfortunately, we have yet to isolate this compound cleanly, as it appears to undergo rapid decomposition even at low temperature. Hence, for the moment, we have not realized the intermolecular version of **23** itself acting as a dienophile.

However, the underlying concept has been realized, in an IMDA setting, with a 4-chlorocyclobutenone dienophile. Allylic alcohol **31** was prepared according to our recently published procedure.[2] Following exposure of the latter to small amounts of BF_3 etherate, there was obtained the DA adduct **33**, with high levels of stereoselectivity (Scheme 5). The course of the progression from **31** → **33** was followed by TLC and NMR. As shown, enone **32** served as an intermediate in this progression. Notably, IMDA reaction of the 4-chloro substrate was significantly more rapid than that of the analogous des-halo substrate. Treatment of crude compound **33** with aqueous sodium hydroxide led, not unexpectedly, to **34**. It is interesting to note that from the perspective of pattern recognition analysis, **34** corresponds to the IMDA product of the hypothetical **35**.

In summary, the logic at the core of the proposal has been reduced to practice. The first examples of halogenated cyclobutenones as an inter- and intramolecular dienophiles are described. It was found that 2-bromocyclobutenone is far more reactive than the parent compound and is equally *endo*-selective. Moreover, we have shown that cyclobutenones are the first class of dienophiles to give exclusive *meta* regiochemistry, in noncatalyzed settings, with Dane's diene. Competition experiments demonstrated that enhancement of the otherwise sluggish dienophilicity of simple cycloalkenones through installation of a bromine atom at the α-carbon of the enone is quite general. Moreover, the resultant cycloadducts undergo ring contraction to provide novel carane derivatives.

EXPERIMENTAL SECTION

General Experimental Methods. All commercial reagents were used without further purification. All solvents were reagent or HPLC grade. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), toluene, and benzene were passed through a column of alumina and used without further drying. All reactions were carried out in flame-dried glassware under an argon or

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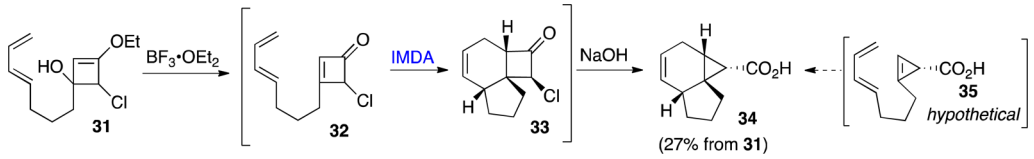
Scheme 5. IMDA Reaction with 4-Chlorocyclobutenone Dienophile



nitrogen atmosphere unless otherwise noted. Analytical TLC was performed on silica gel 60 F254 plates and visualized by UV fluorescence quenching and $KMnO_4$ staining. Flash column chromatography was performed on silica gel 60 (40−63 mm). Yields refer to chromatographically and spectroscopically pure compounds. ^1H NMR and ^{13}C NMR spectra were recorded on a 500 or 600 MHz spectrometer at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to residual solvent $CDCl_3$ (^1H, 7.27 ppm; ^{13}C, 77.00 ppm). Multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, tt = triplet of triplets, m = multiplet, comp m = complex multiplet, q = quartet, app. = apparent, bs = broad singlet. The dr was determined by ^1H NMR analysis. A TOF mass analyzer was used for HRMS measurements.

2-Bromocyclobut-1-enone (3). To a light-protected, 0 °C solution ($CDCl_3$) of cyclobutenone **1** (1.0 equiv, 5 mL, 0.55 M, 2.75 mmol) was added bromine (1.5 equiv, 0.16 mL, 4.1 mmol). After being stirred for 30 min, the solution was concentrated in vacuo to provide **2** as a pale orange oil. Compound **2** was dissolved in fresh $CDCl_3$ (2.75 mL), protected from light, and cooled to 0 °C. Solid Cs_2CO_3 (5.0 equiv, 4.6 g, 13.8 mmol) was added in portions. The heterogeneous mixture was stirred vigorously for 2 h. After warming to ambient temperature, the solution was filtered through a phase separator, to give **3** (0.67 M, 67%): R_f 0.4 (3:1 pentane/diethyl ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (t, J = 0.9 Hz, 1 H), 3.37 (d, J = 0.9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 140.0, 118.7, 49.6; IR (thin film) 2938, 1769, 1524, 1170, 1037, 600 cm^{-1}; EI-HRMS $(M + H)^+$ calcd for C_4H_3BrO 145.9446, found 146.9435; $(M + 2H)^+$ found 146.9418.

(1*S*,5*S*,6*S*)-6-Bromo-3-((*tert*-butyldimethylsilyl)oxy)-5-methoxybicyclo[4.2.0]oct-3-en-7-one (5a). To a solution ($CDCl_3$) of **3** (1.0 equiv, 1 mL, 0.6 M, 0.6 mmol) was added *trans*-1-methoxy-3-(*tert*-butyldimethylsilyl)-1,3-butadiene (**4a**) (1.05 equiv, 135 mg, 0.63 mmol), and the reaction was stirred at ambient temperature. After 3 h, the mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexanes/EtOAc) to provide **5a** (208 mg, 92%) as a colorless gel: R_f 0.3 (10:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (d, J = 3.6 Hz, 1H), 4.28 (d, J = 2.8 Hz, 1H), 3.42 (s, 3H), 3.21 (dd, J = 16.7, 9.1 Hz, 1H), 2.91 (ddd, J = 16.0, 8.6, 3.3 Hz, 1H), 2.84 (dd, J = 16.7, 8.3 Hz, 1H), 2.63−2.55 (m, 1H), 2.26 (dd, J = 16.6, 3.3 Hz, 1H), 0.95 (s, 9H), 0.21 (d, J = 4.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 153.8, 102.7, 81.3, 70.6, 58.4, 50.7, 35.7, 32.4, 26.0, 18.4, −4.0; IR (thin film) 2937, 1788, 1605, 1266, 1061, 612 cm^{-1}; ESI-HRMS $(M + Na)^+$ calcd for $C_{15}H_{25}BrO_3NaSi$ 383.0654, found 383.0640; $(M + 2)^+$ found 385.0620.

(1*S*,5*S*,6*S*)-6-Bromo-3-((*tert*-butyldimethylsilyl)oxy)-5-methylbicyclo[4.2.0]oct-3-en-7-one (5b). To a solution ($CDCl_3$) of **3** (1.0 equiv, 1 mL, 0.6 M, 0.6 mmol) was added (*E*)-*tert*-butyldimethyl(penta-1,3-dien-2-yloxy)silane (**4b**) (1.05 equiv, 125 mg, 0.63 mmol), and the reaction was stirred at ambient temperature. After 6 h, the mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexanes/EtOAc) to provide **5b** (182 mg, 88%) as a colorless gel: R_f 0.3 (10:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 3.44 (dd, J = 17.0, 9.4 Hz, 1H), 3.10−3.03 (m, 1H), 2.85 (dd, J = 17.0, 6.7 Hz, 1H), 2.36−2.28 (m, 1H), 2.27−2.19 (m, 1H), 2.19−2.11 (m, 2H), 1.63 (s, 3H), 0.96 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 145.1, 131.9, 111.2, 101.7, 68.0, 50.5, 41.7, 31.4, 27.7, 26.2, 18.6, 14.5, −3.4; IR (thin film) 2980, 1779, 1645, 1200, 1008, 650 cm^{-1}; EI-HRMS $(M + Na)^+$ calc for $C_{15}H_{25}BrO_2NaSi$ 367.0705, found 367.0707; $(M + 2)^+$ found 369.0684.

(1*S*,5*S*,6*S*)-6-Bromo-5-methoxybicyclo[4.2.0]oct-3-en-7-one (5c). To a solution ($CDCl_3$) of **3** (1.0 equiv, 1 mL, 0.6 M, 0.6 mmol) was added 1-methoxy-1,3-butadiene (**4c**) (1.05 equiv, 64 μL, 0.63 mmol), and the reaction was stirred at ambient temperature. After 3 h, the mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexanes/EtOAc) to provide **5c** (130 mg, 94%) as a bright yellow oil: R_f 0.3 (10:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (q, J = 10.2, 8.2 Hz, 2H), 4.10 (s, 1H), 3.54 (s, 3H), 3.18 (dd, J = 17.7, 9.6 Hz, 1H), 2.94 (q, J = 8.5, 7.6 Hz, 1H), 2.71 (dd, J = 17.7, 8.0 Hz, 1H), 2.53−2.43 (m, 1H), 2.35−2.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 129.3, 127.78, 103.7, 80.6, 59.6, 49.8, 35.5, 26.4; IR (thin film) 2960, 1771, 1618, 1150 cm^{-1}; ESI-HRMS $(M + Na)^+$ calcd for $C_9H_{11}BrO_2Na$ 252.9840, found 252.9942; $(M + 2)^+$ found 254.9926.

(1*S*,6*R*)-6-Bromo-3-methylbicyclo[4.2.0]oct-3-en-7-one (5d). To a solution ($CDCl_3$) of **3** (1.0 equiv, 1 mL, 0.6 M, 0.6 mmol) was added isoprene (**4d**) (10.0 equiv, 600 μL, 6.0 mmol), and the reaction was stirred at ambient temperature. After 20 h, the mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexanes/EtOAc) to provide **5d** (110 mg, 86%) as a colorless oil: R_f 0.3 (15:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.55−5.48 (m, 1 H), 3.36 (dd, J = 18.3, 9.9 Hz, 1 H), 3.14−3.03 (m, 1 H), 2.71 (dd, J = 15.7, 6.9 Hz, 1 H), 2.66−2.55 (m, 1 H), 2.55−2.43 (m, 2 H), 2.11 (dd, J = 16.0, 1.9 Hz, 1 H), 1.78 (ap s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 135.9, 119.6, 67.8, 48.9, 36.2, 32.9, 32.3, 24.5; IR (thin film) 2958, 1782, 1272, 747, 703 cm^{-1}; EI-HRMS $(M)^+$ calcd for $C_9H_{11}BrO$ 213.9993, found 213.9995; $(M + 2)^+$ found 215.9973.

(1*S*,6*R*)-6-Bromo-3,4-dimethylbicyclo[4.2.0]oct-3-en-7-one (5e). To a solution ($CDCl_3$) of **3** (1.0 equiv, 10 mL, 0.6 M, 6.0 mmol) was added 2,3-dimethyl-1,3-butadiene (**4e**) (10.0 equiv, 6.8 μL, 6.0 mmol), and the reaction was stirred at ambient temperature. After 18 h, the mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexanes/EtOAc) to provide **5e** (1.26 g, 92%) as a colorless oil: R_f 0.3 (20:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 3.35 (dd, J = 18.2, 9.9 Hz, 1 H), 3.01 (dtd, J = 10.9, 5.5, 2.0 Hz, 1 H), 2.62 (d, J = 15.3 Hz, 1 H), 2.54 (s, 2 H), 2.48 (dd, J = 18.3, 5.6 Hz, 1 H), 2.09 (ap d, J = 15.5 Hz, 1 H), 1.73 (s, 3 H), 1.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 126.8, 126.2, 68.4, 48.7, 39.1, 36.3, 34.1, 20.4, 19.3; IR (thin film) 2993, 2919, 1787, 670 cm^{-1}; EI-HRMS $(M)^+$ calcd for $C_{10}H_{13}BrO$ 228.0150, found 228.0156; $(M + 2)^+$ found 230.0130.

(1*R*,2*R*,5*S*,6*R*)-6-Bromo-2,5-dimethylbicyclo[4.2.0]oct-3-en-7-one (5f). To a solution ($CDCl_3$) of **3** (1.0 equiv, 1 mL, 0.6 M, 0.6 mmol) was added 2,4-hexadiene (**4f**) (10.0 equiv, 684 μL, 0.6 mmol), and the reaction was stirred at ambient temperature. After 18 h, the mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexanes/EtOAc) to provide **5f** (132.7 mg, 97%) as a colorless oil: R_f 0.4 (9:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (dt, J = 9.5, 2.1 Hz, 1 H), 5.64 (dt, J = 9.5, 2.6 Hz, 1 H), 2.99 (dd, J = 17.6, 9.6 Hz, 1 H), 2.95 − 2.88 (m, 1 H), 2.76 − 2.66 (m, 1 H), 2.65 − 2.55 (m, 1 H), 2.49 (dd, J = 17.6, 6.5 Hz, 1 H), 1.28 (d, J = 7.2 Hz, 3 H), 1.08 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 133.7, 131.6, 74.1, 45.0, 43.1, 38.2, 30.4, 17.4, 16.4; IR (thin film) 2958, 2925, 1723, 1273, 1125, 1074, 742, 699 cm^{-1}; EI-HRMS $(M)^+$ calcd for $C_{10}H_{13}BrO$ 228.0150, found 228.0146; $(M + 2)^+$ found 230.0130.

(2*R*,5*R*)-2-Bromotricyclo[4.2.2.0^{2,5}]dec-7-en-3-one (5g). To a solution ($CDCl_3$) of **3** (1.0 equiv, 1 mL, 0.6 M, 0.6 mmol) was added

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1,3-cyclohexadiene (**4g**) (10.0 equiv, 571 μL, 0.6 mmol), and the reaction was stirred at ambient temperature. After 24 h, the mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexanes/EtOAc) to provide **5g** (122.0 mg, 90%) as a colorless oil: R_f 0.3 (15:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29−6.22 (m, 2H), 3.18 (dd, *J* = 18.3, 9.3 Hz, 1H), 2.85 (ddq, *J* = 29.0, 4.4, 2.3 Hz, 1H), 2.60−2.44 (m, 1H), 2.11- 2.01 (m, 1H), 1.67 (dddd, *J* = 12.1, 9.5, 4.7, 2.4 Hz, 1H), 1.51 (ddd, *J* = 16.3, 8.2, 3.7 Hz, 1H), 1.37−1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 133.1, 132.6, 75.0, 49.2, 39.5, 38.0, 33.6, 24.0, 20.2; IR (thin film) 2967, 2900, 1769, 1275, 1055, 749 cm^{-1}. EI-HRMS (M^+) calcd for $C_{10}H_{11}BrO$ 225.9993, found 226.0010.

(2a*S*,10a*S*)-6-Methoxy-2,2a,3,4,10,10a-hexahydrocyclobuta-[*a*]phenanthren-1(9*H*)-one (7). To a stirred solution of Dane's diene (**6**) (1.2 equiv, 10 mg, 0.05 mmol) in $CDCl_3$ (0.4 μL) at 45 °C was added a solution ($CDCl_3$) of **1** (1.0 equiv, 5 μL, 0.6 M, 0.04 mmol). After being stirred for 24 h, the reaction was concentrated in vacuo. The crude residue was purified by flash column chromatography (4:1, pentane/ether) to provide **7** (7.9 mg, 78%) as a colorless oil: R_f 0.4 (4:1 pentanes/ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.7 Hz, 1 H), 6.74 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.63 (d, *J* = 2.4 Hz, 1 H), 6.32 (dt, *J* = 6.6, 2.9 Hz, 1 H), 3.80 (s, 3 H), 3.54 (tt, *J* = 7.5, 3.5 Hz, 1 H), 2.96 (ddd, *J* = 18.2, 8.9, 4.4 Hz, 1 H), 2.86 (ddd, *J* = 14.3, 9.0, 5.4 Hz, 1 H), 2.84 − 2.71 (m, 2 H), 2.72 − 2.64 (m, 1 H), 2.61 (ddd, *J* = 16.5, 7.4, 1.4 Hz, 1 H), 2.52 (ddd, *J* = 18.1, 5.8, 3.5 Hz, 1 H), 2.25 (ddt, *J* = 16.6, 7.1, 2.9 Hz, 1 H), 1.94 (dq, *J* = 12.3, 3.8 Hz, 1 H), 1.43 (qd, *J* = 12.6, 4.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 158.6, 139.0, 135.4, 127.4, 124.6, 117.9, 113.1, 112.7, 58.4, 55.2, 48.2, 36.4, 30.2, 28.4, 26.7, 23.9; IR (thin film) 3026, 2919, 2833, 1776, 1605, 1496, 1236, 1042 cm^{-1}; EI-HRMS (M^+) calcd for $C_{17}H_{18}O_2$ 254.1307, found 254.1298.[17]

(2a*R*,10a*R*)-10a-Bromo-6-methoxy-2,2a,3,4,10,10a-hexahydrocyclobuta[*a*]phenanthren-1(9*H*)-one (9). To neat Dane's diene (**6**) (1.2 equiv, 74.5 mg, 0.4 mmol) at 23 °C was added a solution ($CDCl_3$) of **3** (1.0 equiv, 1 μL, 0.2 M, 0.2 mmol). After being stirred 2 h, the reaction was directly purified by flash column chromatography (10:1, pentane/ether) to provide **9** (39.7 mg, 91%) as a colorless oil: R_f = 0.64 (3:1 pentane/diethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.5 Hz, 1 H), 6.75 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.71 (d, *J* = 2.6 Hz, 1 H), 3.81 (s, 3 H), 3.55 (dd, *J* = 17.1, 9.8 Hz, 1 H), 3.23−3.15 (m, 1 H), 2.95 (dd, *J* = 17.1, 6.6 Hz, 1 H), 2.79 (qt, *J* = 15.5, 7.8 Hz, 2 H), 2.65−2.46 (m, 2 H), 2.34−2.15 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 158.5, 136.7, 129.7, 128.2, 128.0, 123.3, 113.7, 111.1, 68.0, 55.2, 50.3, 40.5, 30.1, 28.4, 26.9, 22.0; IR (thin film) 3001, 2932, 2834, 1789, 1608, 1500, 1251, 1040, 818 cm^{-1}; EI-HRMS (M +) calcd for $C_{17}H_{17}O_2Br$ 322.0412, found 332.0409; $(M + 2)^+$ found 334.0393.

(4a*R*,8a*R*)-8a-Bromo-6,7-dimethyl-3,4,4a,5,8,8a-hexahydronaphthalen-1(2*H*)-one (15). A stirred solution of cyclohexenone (**11**) (1.0 equiv, 192 mg, 2 mmol), 2-bromocyclohexenone (**12**) (1.0 equiv, 350 mg, 2 mmol), and 2,3-dimethyl-1,3-butadiene (**13**) (1.0 equiv, 226 μL, 2 mmol) in toluene (40 mL) was warmed to 120 °C. After 12 h, the reaction mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (19:1, hexanes/EtOAc) to provide **15** (281 mg, 55%) as a red solid. Spectral data agreed with known characterization.[11]

(3a*R*,7a*R*)-7a-Bromo-5,6-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one (19). A stirred solution of cyclopentenone (**16**) (1.0 equiv, 164 mg, 2 mmol), 2-bromocyclopentenone (**17**) (1.0 equiv, 320 mg, 2 mmol), and 2,3-dimethyl-1,3-butadiene (**13**) (1.0 equiv, 226 μL, 2 mmol) in toluene (40 mL) was warmed to 120 °C. After 12 h, the reaction mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (19:1, hexanes/EtOAc) to provide **19** (333 mg, 69%) as a pale yellow solid. Spectral data agreed with known characterization.[11]

(1*S*,6*R*)-6-Bromo-3,4-dimethylbicyclo[4.2.0]oct-3-en-7-one (5e). A solution of cyclobutenone (**1**) (1.0 equiv, 1 mL, 0.7 M, 0.7 mmol), 2-bromocyclobutenone (**3**) (1.0 equiv, 1 mL, 0.7 M, 0.7 mmol), and 2,3-dimethyl-1,3-butadiene (**13**) (1.0 equiv, 80 μL, 0.7 mmol) in $CDCl_3$ was stirred at ambient temperature. After 12 h, the reaction mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (19:1, hexanes/EtOAc) to provide **5e** (105 mg, 70%) as a colorless oil. Spectral data agreed with those described above.

(4a*R*,8a*R*)-8a-Bromo-6,7-dimethyl-3,4,4a,5,8,8a-hexahydronaphthalen-1(2*H*)-one (15). A stirred solution of cyclohexenone (**11**) (1.0 equiv, 192 mg, 2 mmol) and 2-bromocyclohexenone (**12**) (1.0 equiv, 350 mg, 2 mmol) in CH_2Cl_2 (40 mL) was lowered to −10 °C. $MeAlCl_2$ (0.1 equiv, 21 μL, 0.2 mmol) was added, and the reaction stirred for 15 min. 2,3-Dimethyl-1,3-butadiene (**13**) (1.0 equiv, 80 μL, 0.7 mmol) was added and the reaction stirred 2 h while warming to ambient temperature. The mixture was cooled to 0 °C and treated with Rochelle's salt. The layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2. The organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1, hexane/ethyl acetate) to provide **15** (372 mg, 87%) as a red solid. Spectral data agree with known characterization.[11]

(1a*R*,9a*S*)-5-Methoxy-1a,2,3,8,9,9a-hexahydro-1*H*-cyclopropa[*a*]phenanthrene-9a-carboxylic Acid (21a). Cycloadduct **9** (1 equiv, 33 mg, 0.1 mmol) was dissolved in CH_3CN (2 mL) at ambient temperature. Aqueous NaOH (1.0 mL, 1.0 M) was added dropwise. The clear, colorless solution quickly developed an intense yellow color upon addition of base and became red over several minutes. After 5 min, the reaction was quenched by the addition of aqueous HCl (1 mL, 1.0 M). The aqueous mixture was extracted with Et_2O, and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1, pentane/ether) to provide **21a** (22 mg, 80%) as a colorless oil: R_f = 0.54 (1:1 pentane/diethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 8.3 Hz, 1 H), 6.74−6.67 (m, 2 × 1 H overlapping), 3.79 (s, 3 H), 2.80 (td, J = 14.3, 6.9 Hz, 1 H), 2.70 (dt, J = 15.2, 5.7 Hz, 1 H), 2.60−2.51 (m, 1 H), 2.51−2.39 (m, 1 H), 2.37−2.25 (m, 2 H), 2.16−2.01 (m, 2 H), 1.95 (dd, J = 9.0, 5.6 Hz, 1 H), 1.64 (dd, J = 9.0, 4.1 Hz, 1 H), 1.30−1.24 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 157.9, 136.8, 131.0, 128.8, 124.6, 122.8, 113.6, 110.9, 55.3, 29.3, 28.7, 26.9, 26.1, 21.0, 20.3, 19.5; IR (thin film) 2929, 1682, 1498, 1429, 1250 cm^{-1}; FAB-HRMS (M^+) calcd for $C_{17}H_{18}O_3$ 270.1256, found 270.1266.

(1*R*,6*S*)-4-Methylbicyclo[4.1.0]hept-3-ene-1-carboxylic Acid (21b). Cycloadduct **5d** (1 equiv, 21 mg, 0.1 mmol) was dissolved in CH_3CN (2 mL) at ambient temperature. Aqueous NaOH (1.0 mL, 1.0 M) was added dropwise. After 5 min, the reaction was quenched by the addition of aqueous HCl (1 mL, 1.0 M). The aqueous mixture was extracted with Et_2O, and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1, pentane:ether) to provide **21b** (14.5 mg, 67%) as a colorless oil: R_f = 0.59 (1:1 pentane/diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 1 H), 2.83−2.73 (m, 1 H), 2.44−2.34 (m, 2 H), 2.19 (d, *J* = 18.5 Hz, 1 H), 1.91−1.71 (m, 2 H overlapping), 1.62 (s, 3 H), 1.31 (dd, *J* = 9.2, 3.5 Hz, 1 H), 0.91 (dd, *J* = 6.6, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 128.8, 117.2, 28.7, 24.4, 23.6, 22.6, 21.7, 17.5; IR (thin film) 3422 (br), 3024, 2961, 1771 cm^{-1}; EI-HRMS (M^+) calcd for $C_9H_{12}O_2$ 152.0837, found 152.0830.

(1*R*,6*S*)-3,4-Dimethylbicyclo[4.1.0]hept-3-ene-1-carboxylic Acid (21c). Cycloadduct **5e** (1 equiv, 23 mg, 0.1 mmol) was dissolved in CH_3CN (2 mL) at ambient temperature. Aqueous NaOH (1.0 mL, 1.0 M) was added dropwise. After 5 min, the reaction was quenched by the addition of aqueous HCl (1 mL, 1.0 M). The aqueous mixture was extracted with Et_2O, and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1, pentane/ether) to provide **21c** (15.2 mg, 72%) as a colorless oil: R_f = 0.57 (1:1 pentane/diethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.74 (d, *J* = 17.6 Hz, 1 H), 2.43 (d, *J* = 17.3 Hz, 1 H), 2.23 (dd, *J* = 35.5, 17.4 Hz, 2 H), 1.78 (dd, *J* = 9.9, 5.1 Hz, 1 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.3−1.25 (m, 1 H), 0.88−0.82 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 121.8, 120.5, 30.7, 30.5, 22.8, 22.6, 19.2, 19.1, 17.6; IR

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(thin film) 3000, 2917, 1684, 1438, 1303, 1226 cm^{-1}; EI-HRMS (M^+) calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.1002.

(1*R*,2*R*,5*S*,6*R*)-6-Hydroxy-2,5-dimethylbicyclo[4.2.0]oct-3-en-7-one (21d). Cycloadduct **5f** (1 equiv, 23 mg, 0.1 mmol) was dissolved in CH_3CN (2 mL) at ambient temperature. Aqueous NaOH (1.0 mL, 1.0 M) was added dropwise. After 5 min, the reaction was quenched by the addition of aqueous HCl (1 mL, 1.0 M). The aqueous mixture was extracted with Et_2O, and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1, pentane/ether) to provide **21d** (11.7 mg, 56%) as a colorless oil: R_f = 0.24 (1:1 pentane/diethyl ether); ^1H NMR (500 MHz, $CDCl_3$) δ 5.59 (s, 2 H), 2.72 (dd, J = 12.4, 8.4 Hz, 1 H), 2.69–2.60 (m, 1 H), 2.47–2.35 (m, 2 H), 2.35–2.28 (m, 1 H), 1.14 (d, J = 7.4 Hz, 3 H), 1.08 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 132.3, 131.2, 94.3, 42.8, 40.8, 36.6, 30.6, 18.2, 15.7; IR (thin film) 3422, 3024, 2961, 1771, 1456, 1376, 1135, 1067 cm^{-1}; FAB-HRMS (M^+) calcd for $C_{10}H_{13}O_2$ 165.0916, found 165.0908.

4-Bromo-3-ethoxycyclobut-2-enone (29). To a solution of ethoxyacetylene (1.0 equiv, 0.697 g, 4.6 mmol) in hexanes (10 mL) at −78 °C were added Et_2O (10 mL) and Et_3N (2.0 equiv, 1.25 mL, 8.97 mmol). The resulting solution was stirred for 5 min followed by the addition of bromoacetyl bromide **28** (2.0 equiv, 0.71 mL, 8.9 mmol) over 2 min. The resulting white suspension was allowed to warm to room temperature over 14 h and filtered through a pad of Celite with the aid of additional Et_2O. The organics were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1, pentane/ether) to provide cyclobutenone **29** (362 mg, 54%) as a red oil: R_f = 0.3 (4:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, J = 0.9 Hz, 1H), 5.16 (d, J = 0.9 Hz, 1H), 4.35 (q, J = 7.0 Hz, 2H), 1.52 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 179.7, 110.9, 70.9, 65.9, 14.2; IR (thin film) 3097, 2987, 2901, 1774, 1585, 1469, 1400, 1324, 1215, 1025 cm^{-1}; EI-HRMS (M^+) calcd for $C_6H_7BrO_2$ 189.9629, found 189.9634; $(M + 2)^+$ found 191.9622.

4-Bromocyclobut-2-enone (30). To a toluene (10 mL) solution of **29** (1 equiv, 189 mg, 1 mmol) at −78 °C was added DIBAL-H (1 equiv, 1 mL, 1.0 M, 1 mmol) over 15 min. As the mixture warmed to ambient temperature, Rochelle's salt (20 mL) was added and stirred for 2 h. When the mixture was sufficiently solubilized, it was extracted with Et_2O. The combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was filtered through a long plug of Celite and concentrated to give **30** (96 mg, 52%) as a dark orange gel: R_f = 0.1 (4:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (dd, J = 3.2, 2.4, 1H), 4.91–4.85 (m, 1H), 4.58 (d, J = 3.0 Hz, 1 H), 4.01–3.84 (m, 2 H), 1.33 (t, J = 7.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 103.9, 65.6, 65.1, 56.5, 14.1; IR (thin film) 3179, 2985, 1630, 1313, 1075, 1032 cm^{-1}; EI-HRMS (M^+) calcd for $C_6H_9BrO_2$ 191.9786, found 191.9790; $(M + 2)^+$ found 193.9765.

(1*R*,1a*R*,4a*R*,7a*R*)-1a,2,4a,5,6,7-Hexahydro-1*H*-cyclopropa[*d*]indene-1-carboxylic Acid (34). Compound **31** (1 equiv, 24 mg, 0.1 mmol) was dissolved in $CDCl_3$ (1 mL) at ambient temperature and treated with 1 drop of $BF_3{\cdot}OEt_2$. After 30 min, **32** could be observed by NMR. The reaction was allowed to continue for an additional 6 h to provide **33**, which was concentrated in vacuo. A crude solution of **33** (1.0 equiv, 19.6 mg, 0.1 mmol) was dissolved in CH_3CN (2 mL) at ambient temperature. Aqueous NaOH (1.0 mL of a 1.0 M solution) was added dropwise. The clear, colorless solution quickly developed an intense yellow color upon addition of base, then became red over several minutes. After 30 min, the reaction was quenched by the addition of aqueous HCl (1.0 M), which decolorized the solution. The aqueous mixture was extracted with Et_2O and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (10:1 pentane/Et_2O) to provide **34** (5.3 mg, 27% from **31**) as a colorless oil: R_f = 0.3 (1:1 pentane/diethyl ether); ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (d, J = 9.8 Hz, 1 H), 5.46 (td, J = 6.4, 3.0 Hz, 1 H), 2.44–2.31 (m, 2 H), 2.10 (s, 1 H), 1.96–1.85 (m, 2 H), 1.82 (d, J = 3.5 Hz, 1 H), 1.80–1.63 (m, 2 H), 1.41–1.28 (m, 1 H), 1.24 (d, J = 9.7 Hz, 1 H), 0.87–0.80 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 127.8, 123.8, 41.2, 30.3, 27.4, 26.1, 25.3, 24.7, 21.7, 21.4; IR (thin film) 3011, 2947, 1681, 1420, 1287 cm^{-1}; EI-HRMS (M^+) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0999.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic and analytical data for new compounds. 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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■ DEDICATION

This paper is dedicated to the great accomplishments of Robert Ireland in advancing the horizons of organic synthesis.

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