

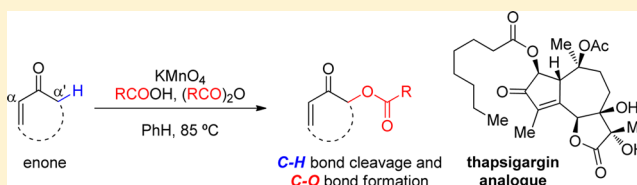
Acyloxylation of Cyclic Enones: Synthesis of Densely Oxygenated Guaianolides

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S Supporting Information

ABSTRACT: The α' -acyloxylation of cyclic enones with linear carboxylic acids is described. The reaction is promoted by KMnO_4 in the presence of a carboxylic acid and its corresponding carboxylic anhydride. The optimization of the reaction has been carried out using the statistical methodology known as design of experiments. The optimized reaction conditions have been evaluated in terms of substrate scope and compatibility with different functional groups. The methodology has been applied to the synthesis of densely oxygenated guaianes and guaianolides.



INTRODUCTION

In the last decades, different methodologies for the activation of C–H bonds have emerged.¹ Remarkable progress has been made in the $\text{C}(\text{sp}^2)$ –H activation (aromatic or vinylic)² and in the oxidation of $\text{C}(\text{sp}^3)$ –H bonds at allylic positions.³ Another interesting reaction involving the transformation of $\text{C}(\text{sp}^3)$ –H bonds is the α -oxidation of a carbonyl group. This kind of reaction has been the subject of research since many biologically significant compounds bear either hydroxyl or acyloxy groups in this position.⁴

In 1989, Watt et al. reported that enones could be functionalized at the α' -position by treatment with $\text{Mn}(\text{OAc})_3$ in the presence of different carboxylic acids.⁵ The mechanism involves the *in situ* generation of a radical $\text{Mn}(\text{III})$ carboxylate, which reacts with the enone, leading to the corresponding α' -acyloxyenone.⁶ Although good yields were reported, the methodology presented some problems: (i) the need for a large excess of the carboxylic acid and the Mn precursor, which, in addition, had to be freshly prepared⁷ or dried prior to use; (ii) the use of a Dean–Stark trap to remove the water, which made scaling up or down the reaction difficult; and (iii) poor functional group compatibility.

Demir et al. reported some improvements by using KMnO_4 instead of $\text{Mn}(\text{OAc})_3$ to generate the $\text{Mn}(\text{III})$ species *in situ*.⁸ Yet, the scope of the reaction was rather limited and the application of this methodology to the synthesis of natural products remained a challenge. References applying this method into complex syntheses are lacking, and the reproducibility issues and some contradictory results have prevented this reaction to be included in the pool of synthetically useful reactions.

Herein, we present our study and optimization of the α' -acyloxylation of cyclic enones by KMnO_4 in the presence of a mixture of a carboxylic acid and its corresponding anhydride as an effective water scavenger. The use of Dean–Stark apparatus

is no longer necessary, simplifying the scaling of the reaction. The reaction conditions have been optimized using a design of experiments (DoE) approach,⁹ which guarantees the robustness of the method. The optimized reaction conditions have been applied to the synthesis of several guaianes and guaianolides, closely related to thapsigargin **1a** and thapsigarginin **1b**, two compounds with remarkable anti-SERCA ATPase activity (Figure 1).¹⁰

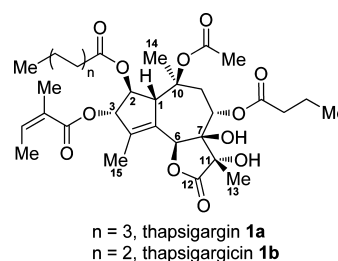


Figure 1. Thapsigargin **1a** and thapsigarginin **1b**.

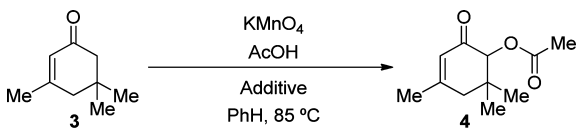
RESULTS AND DISCUSSION

In the seminal report by Watt, it was demonstrated that removal of water was necessary for the reaction to proceed.⁵ When we first ran the reaction using small amounts of the reactants, the Dean–Stark trap was not effective. The collected solvent in the side arm of the trap was cloudy, but the amount of water generated was too small to become an isolated aqueous layer. To solve this problem and simplify the reaction setup, we undertook an exploratory screening of methods to remove efficiently the generated water. As a benchmark

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Table 1. Screening of Conditions without a Dean–Stark Apparatus^a


entry	time prior to substrate addition (min)	temp (°C)	KMnO ₄ (equiv)	AcOH (equiv)	additive	yield ^b (%)
1	60	85	1.20	10	4 Å MS (0.060 g)	39
2	30	85	3.10	25	4 Å MS (0.230 g)	10
3	60	50	2.10	12	4 Å MS (0.230 g)	1
4	45	65	2.10	17	4 Å MS (0.140 g)	12
5	60	85	3.10	25	4 Å MS (0.230 g)	30
6	45	65	2.10	170	4 Å MS (0.140 g)	17
7	30	85	3.10	170	Na ₂ SO ₄ (10 equiv)	37
8	30	85	3.10	170	Ac ₂ O (100 equiv)	63
9	30	85	3.10	170	AcCl (100 equiv)	32

^aReaction conditions: KMnO₄, AcOH, additive, and PhH (4 mL) at the stated temperature and stir for the indicated time, then isophorone 3 (0.025 mL, 0.160 mmol) and stir overnight at the stated temperature. ^bDetermined by GC analysis.

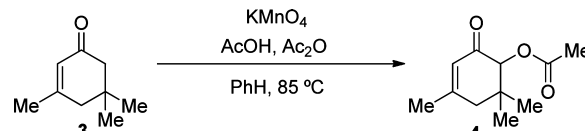
reaction, we chose the α' -acetoxylation of isophorone 3 to produce 6-acetylisophorone 4. We considered five variables to study: (i) time prior to the substrate addition, needed for the formation of the radical Mn(III) carboxylate, (ii) temperature, (iii) equivalents of KMnO₄, (iv) equivalents of acetic acid, and (v) amount of 4 Å molecular sieves. As illustrated in Table 1 (entries 1–6), the use of 4 Å molecular sieves resulted in poor yields presumably due to the high temperature.¹¹ Other additives were also evaluated for the same role, among them acetic anhydride. The reduction of Mn(VII) to Mn(III) involves the formation of water.⁸ The use of a carboxylic anhydride might favor the reaction by removing water and serve as well as an acyloxy group source, along with the carboxylic acid itself. As expected, higher yields were obtained when acetic anhydride was used in conjunction with acetic acid (entry 8, Table 1).

Since the actual mechanism of the reaction remained unclear, we considered the use of a design of experiments (DoE) approach for the optimization of the reaction to be convenient. DoE is a statistical optimization method that explores an experimental domain, setting up different variables or factors in high, medium, and low levels. The influence of these variables is thus studied, and the response (yield in our case) is optimized. Instead of optimizing one variable at a time (an OVAT approach), DoE performs the optimization of several variables simultaneously. An algorithm suggests the conditions in which the experiments have to be run. The response is evaluated, and a model for the behavior of the system is obtained.⁹ The aim is to get the maximum amount of information using the minimum number of experiments.

Our model would take into account three variables: (i) equivalents of KMnO₄, (ii) equivalents of acetic acid, and (iii) equivalents of acetic anhydride. To ensure the effective formation of the radical Mn(III) carboxylate, the time prior to the addition of the substrate and the temperature were set at 30 min and 85 °C, respectively. Finally, the substrate concentration was kept at 0.04 M in benzene. We decided to perform a Box–Behnken design (BBD), with three levels for each variable (Table 2). The experiments were carried out according to the matrix shown in Table 3. The yields were measured, and a quadratic model was fitted for the reaction. The variance of the method was estimated by running three replicates of the central point (Table 3, entries 4, 8, 10, and 11).

Table 2. Selected Levels for Each Variable for BBD

variables	symbol	levels		
		low	medium	high
equiv of KMnO ₄	A	1.05	2.10	3.15
equiv of AcOH	B	10.0	22.5	35.0
equiv of Ac ₂ O	C	5.00	9.50	14.0

Table 3. Design of Experiments Optimization for α' -Acetoxylation of Isophorone 3^{a,b}


run	variables			yield ^c (%)
	A	B	C	
	KMnO ₄ (equiv)	AcOH (equiv)	Ac ₂ O (equiv)	
1	3.15	22.5	5.00	45
2	3.15	10.0	9.50	34
3	1.05	35.0	9.50	86
4	2.10	22.5	9.50	56
5	1.05	22.5	5.00	63
6	3.15	22.5	14.0	51
7	2.10	35.0	5.00	71
8	2.10	22.5	9.50	69
9	3.15	35.0	9.50	67
10	2.10	22.5	9.50	75
11	2.10	22.5	9.50	65
12	2.10	10.0	14.0	48
13	2.10	10.0	5.00	40
14	2.10	35.0	9.50	91
15	1.05	22.5	14.0	58
16	1.05	10.0	9.50	62
17	2.10	35.0	14.0	73

^aReaction conditions: KMnO₄ (variable A), AcOH (B), and Ac₂O (C) in the indicated amounts, and PhH (4 mL) at 85 °C for 30 min, then isophorone 3 (0.025 mL, 0.160 mmol), stirring at 85 °C overnight.

^bRuns displayed in the order determined by the Box–Behnken matrix.

^cDetermined by GC analysis.

According to the results, the optimal conditions were those corresponding to 2.10 equiv of KMnO₄, 35.0 equiv of acetic

acid, and 9.50 equiv of acetic anhydride, which afforded a 91% yield by GC analysis (entry 14, Table 3; 100% isolated yield). As an alternative to the use of benzene, other solvents were evaluated. Moderate yields were obtained with dichloroethane (62%) and toluene (59%). Cyclohexene and acetonitrile afforded lower yields (45% and 35%, respectively).

The obtained model is illustrated by the calculated response surface (Figure 2), which represents the dependence of the

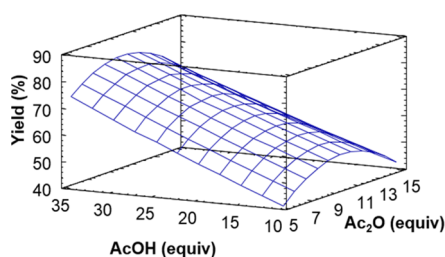


Figure 2. Calculated response surface for the yield of **4** (medium level of KMnO_4 , 2.10 equiv).

yield on the studied variables. An inspection of Figure 2 shows that, for an intermediate level of KMnO_4 , the combination of an intermediate level of acetic anhydride with high levels of acetic acid would lead to higher responses. In addition, the Pareto plot confirms the influence of the acetic anhydride in the system, since its quadratic effect (CC) is significant at 90% confidence (Figure 3). Other interaction effects among variables (AA, AC, AB, BC, and BB) were not significant. As expected, higher amounts of acetic acid lead to higher yields.

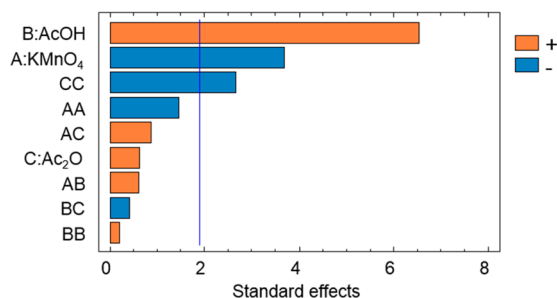


Figure 3. Pareto plot for standard effects over the yield of **4**.

The statistical significance of the model was evaluated by analysis of variance (ANOVA) and the calculation of the coefficient of determination R^2 (Table 4). Although the F value of the model, 3.46, was not high enough to ensure significance at 90% confidence (F was lower than the critical F value, 3.90), the R^2 coefficient was 0.9122, which implied a good fit between predicted and experimental data. The model explained the 95.51% of the variance. Furthermore, the F value for the lack of

fit, 2.49 ($<F_c$), indicated that it was not significant relative to pure error. These results allowed us to consider the model as robust and the obtained optimal conditions as reproducible.

The scope of the reaction was further investigated. Several substrates and linear carboxylic acids with chains of different lengths (2, 4, 6, and 8 carbon atoms) were selected (Table 5). The yields ranged from good to excellent, but no trend attributable to the substrate or the chain length was observed.

We next turned to study the reaction with more complex substrates. Guaianes constitute a widely distributed group of sesquiterpenes, many of which bear a cyclopentenone system. Most guaianolides isolated from Umbelliferae plants display an acyl group located at the C-2 carbon atom, which we envisaged that could be set by α' -oxidation of a ketone previously located at C-3. They seemed a suitable scaffold for the testing of the reaction in a more complex environment. We then decided to test guaianolide **21** and guaiane **25** as substrates for this methodology.

O-Acetylphotosantonin lactone **21** was easily prepared by photochemical rearrangement in 38% yield from α -santonin **20** using AcOH as the solvent (Scheme 1a).¹² On the other hand, guaiane **25** is an intermediate that can be prepared by following a methodology that we devised for the synthesis of analogues of thapsigargin.¹³ To this end, compound **23** was subjected to photochemical rearrangement in AcOH, providing **24** in 72% yield. Subsequent protection of the primary hydroxyl group with TBDMSCl and imidazole afforded guaiane **25** in almost quantitative yield (Scheme 1b).

The behavior of compounds **21** and **25** under the oxidation conditions demonstrated the tolerance of the reaction to the presence of different functional groups such as lactones, esters, double bonds, and silyl protected hydroxyl groups (Table 6). The reaction outcome was affected by substrate stereochemical control, since one single diastereomer was detected in all cases. Structural features in derivatives **26–29** make them interesting from a biological perspective since many sesquiterpene lactones are lead compounds in drug discovery.¹⁴

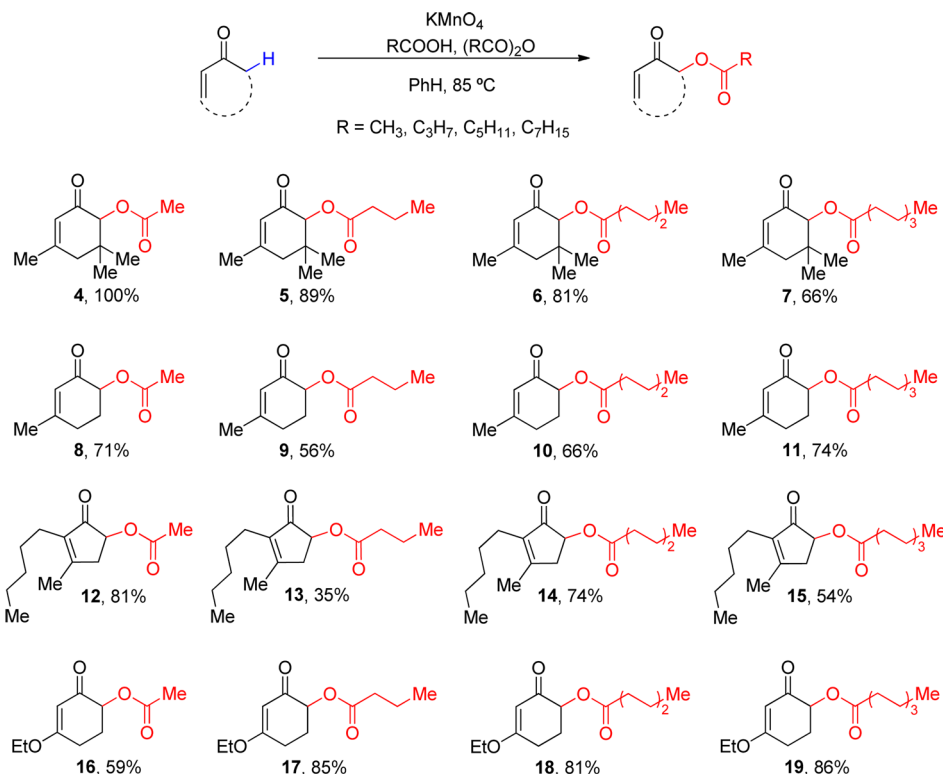
Our interest in bioactive guaianolides prompted us to apply this methodology to the synthesis of new analogues of thapsigargin **1a** and thapsigargin **1b**. There is just one reported total synthesis of thapsigargin and several members of the family by Ley et al.¹⁵ Some unnatural derivatives have been also synthesized by the same authors.¹⁶ Currently, a prodrug¹⁷ against prostate cancer based on thapsigargin is being tested in clinical trials.¹⁸ The remarkable biological activities of thapsigargin and related compounds and the scarcity of methods for their preparation make the opening of new routes of synthesis interesting.

Compound **33** could be conveniently modified to provide thapsigargin analogues (Scheme 2). To this end, **33** was prepared from **25** on a 1 g scale with good yield (see the Experimental Section). Then, it was submitted to TBAF

Table 4. ANOVA Results of the Quadratic Model for the Yield of **4**^a

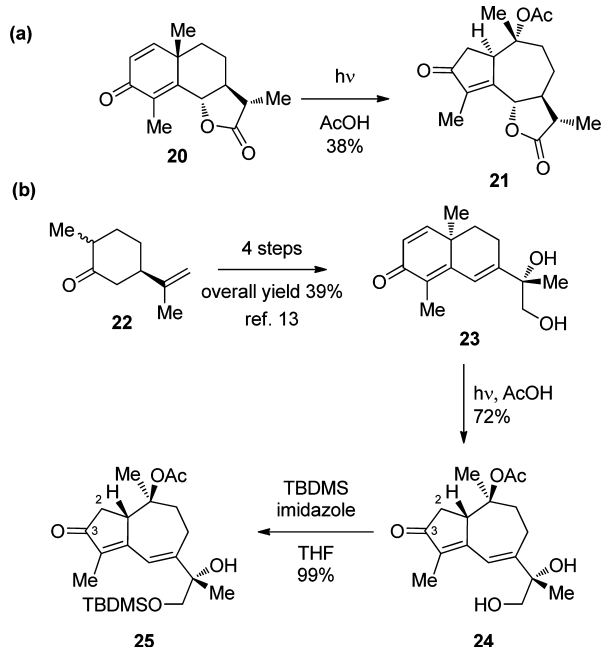
source	sum of squares	degree of freedom	mean squares	F values	F_c values
total	3861.87	16			
model	3522.67	12	293.56	3.46	3.90
residual	339.20	4	84.80		
lack of fit	153.86	1	153.86	2.49	5.54
pure error	185.35	3	61.78		

^a $R^2 = 0.9122$; $R = 0.9551$. 95.51% of the variance explained by the model.

Table 5. Scope of the Reaction of α' -Acyloxylation of Enones^{a,b}

^aReaction conditions: KMnO_4 (83 mg, 0.525 mmol, 2.10 equiv), carboxylic acid (35.0 equiv), and carboxylic anhydride (9.50 equiv) in PhH (6.25 mL) at 85°C for 30 min, then substrate (0.250 mmol) addition and stirring overnight at 85°C . ^bIsolated yields determined after flash column chromatography.

Scheme 1. Preparation of Starting Materials 21 and 25



deprotection, affording diol 34 in 61% yield. Treatment of 34 with NMO in the presence of catalytic OsO_4 produced the dihydroxylation of the C6–C7 double bond, providing tetrol 35, whose purification resulted to be troublesome. The unpurified tetrol 35 was treated with the TEMPO/ NaClO / NaClO_2 oxidation system, leading to guaianolide 36 in 65%

yield (two steps). Guaianolide 36 displays six out of the eight chiral centers found in thapsigargin, thus becoming an interesting model for biological testing.

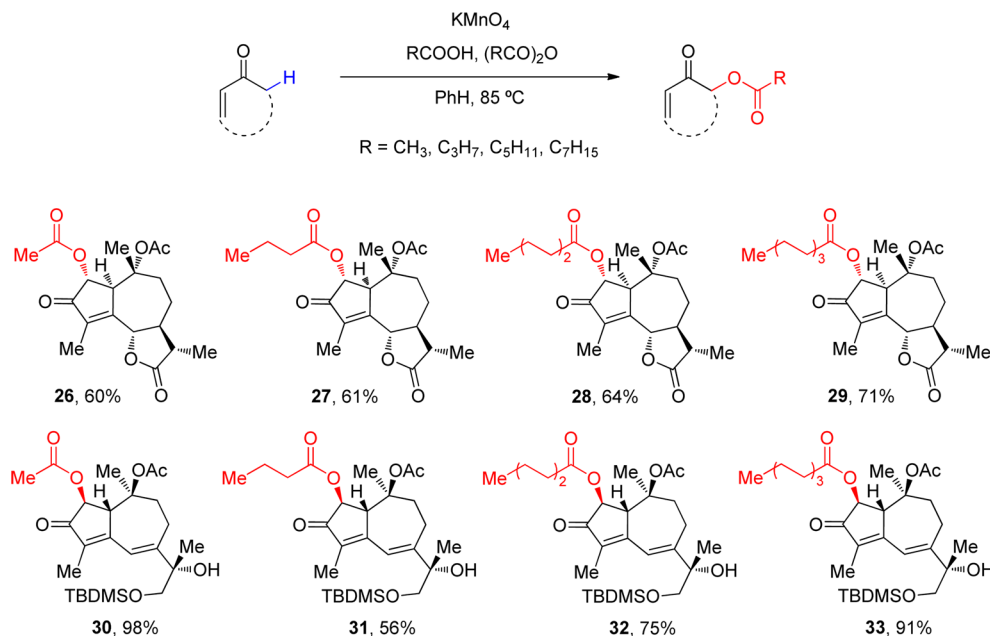
CONCLUSION

We have demonstrated that the use of KMnO_4 in the presence of a carboxylic acid and its corresponding anhydride is a valid method to perform the introduction of an acyl moiety at the α' -position of a carbonyl group, enabling the functionalization of hindered enones. The presence of a carboxylic anhydride makes the use of molecular sieves or a Dean–Stark trap to remove the water unnecessary. In addition, the existence of modern statistics software packages makes the DoE analysis available as a tool for the optimization of chemical reactions. The developed conditions have allowed us to prepare highly oxygenated guaianes and guaianolides that can serve as thapsigargin analogues. Further applications to the synthesis of guaianolide derivatives and their biological evaluation are currently in progress.

EXPERIMENTAL SECTION

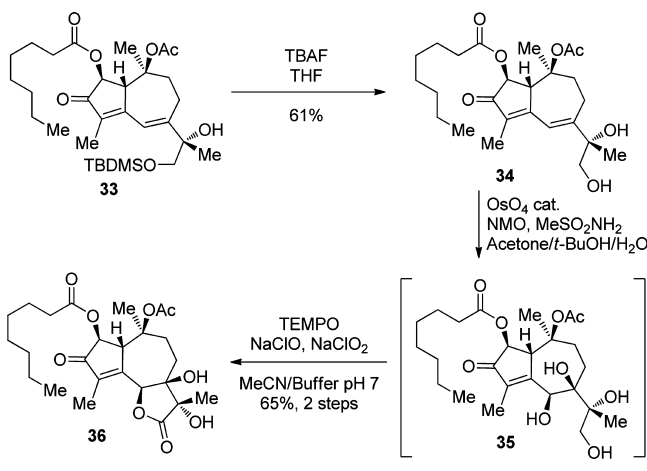
General Methods. HPLC purification was carried out using a 1×25 cm silica gel column (LiChrosorb Si 60, $7 \mu\text{m}$ particle size). GC analyses were performed using a DB-5 column. NMR spectra were recorded on a 400 or 500 MHz spectrometer using standard pulse sequences. Spectra were referenced internally to residual solvent signals (CHCl_3 , $\delta = 7.26$ ppm for ^1H NMR, $\delta = 77.16$ ppm for ^{13}C NMR). Mass spectra were recorded in a UPLC-QTOF mass spectrometer.

Design of Experiments Optimization (Table 3). All experiments were carried out simultaneously in a parallel synthesis carousel. In each vessel, KMnO_4 (amounts according to Table 3) was vigorously

Table 6. Scope of the Reaction over Guaianolide and Guaiane Scaffolds^{a,b}

^aReaction conditions: KMnO_4 (83 mg, 0.525 mmol, 2.10 equiv), carboxylic acid (35.0 equiv), and carboxylic anhydride (9.50 equiv) in PhH (6.25 mL) at 85°C for 30 min, then substrate (0.250 mmol) and stir at 85°C overnight. ^bIsolated yields determined after flash column chromatography.

Scheme 2. Synthesis of Compound 36 from 33



stirred in dry benzene (3 mL). The mixture was heated at 85°C , and the corresponding amounts of acetic acid and acetic anhydride were added. After 30 min, the color changed from purple to brown and a solution of isophorone 3 (0.025 mL, 0.160 mmol) and octadecane (GC internal standard, 5 mg) in dry benzene (1 mL) was added to each vessel. Reactions were vigorously stirred overnight at 85°C . To determine yields by GC, aliquots from the reaction mixture were taken, filtered through silica gel, and analyzed by GC.

Typical Procedure for α' -Acyloxylation of Enones (Tables 5 and 6). To a suspension of KMnO_4 (83 mg, 0.525 mmol, 2.10 equiv) in dry benzene (6.25 mL, 0.04 M in enone) at 85°C were added the corresponding carboxylic acid (8.750 mmol, 35.0 equiv) and its anhydride (2.375 mmol, 9.50 equiv). The mixture was vigorously stirred until the suspension changed from purple to brown (30 min), and then, the enone (0.250 mmol) was added (directly by syringe or dissolved in the minimum amount of dry benzene). Vigorous stirring of the reaction was continued at 85°C overnight, then cooled to room temperature, and filtered through an Al_2O_3 /Celite pad rinsing with EtOAc. The solvent was evaporated under reduced pressure, and the crude oil was purified by flash column chromatography with EtOAc/

hexanes mixtures as eluents to lead to products in yields according to Tables 5 and 6.

6-Acetyloxy-3,5,5-trimethylcyclohex-2-enone (4). Yellow oil (49 mg, 100%); ^1H NMR (500 MHz, CDCl_3) δ 5.87 (br s, 1H), 5.18 (s, 1H), 2.50 (d, $J = 18.4$ Hz, 1H), 2.17 (s, 3H), 2.15 (d, $J = 16.2$ Hz, 1H), 1.92 (s, 3H), 1.06 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.2, 170.6, 159.5, 124.7, 80.6, 46.1, 37.7, 27.3, 24.4, 20.8, 20.0; IR (film) ν_{max} 2970, 2933, 1749, 1688, 1634, 1380, 1234, 1069 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 197.1178; found 197.1177.

6-Butanoyloxy-3,5,5-trimethylcyclohex-2-enone (5). Yellow oil (50 mg, 89%); ^1H NMR (400 MHz, CDCl_3) δ 5.89 (br s, 1H), 5.22 (s, 1H), 2.53 (d, $J = 18.4$ Hz, 1H), 2.45 (m, 2H), 2.17 (d, $J = 18.4$ Hz, 1H), 1.94 (s, 3H), 1.73 (tt, $J = 7.4, 7.4$ Hz, 2H), 1.08 (s, 3H), 1.00 (t, $J = 7.4$ Hz, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.4, 173.3, 159.3, 124.9, 80.4, 46.2, 37.9, 36.2, 27.4, 24.4, 20.1, 18.9, 13.8; IR (film) ν_{max} 2968, 2937, 2876, 1743, 1688, 1636, 1381, 1238, 1176, 1094 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_3$ [M] $^+$ 224.1412; found 224.1425.

6-Hexanoyloxy-3,5,5-trimethylcyclohex-2-enone (6). Yellow oil (51 mg, 81%); ^1H NMR (400 MHz, CDCl_3) δ 5.88 (br s, 1H), 5.20 (s, 1H), 2.51 (d, $J = 19.1$ Hz, 1H), 2.45 (m, 2H), 2.16 (d, $J = 18.4$ Hz, 1H), 1.93 (s, 3H), 1.64 (tt, $J = 7.5, 7.4$ Hz, 2H), 1.34 (m, 4H), 1.06 (s, 3H), 0.96 (s, 3H), 0.88 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.3, 173.4, 159.3, 124.8, 80.3, 46.2, 37.8, 34.2, 31.4, 27.4, 24.8, 24.4, 22.4, 20.1, 14.0; IR (film) ν_{max} 2961, 2934, 2873, 1744, 1690, 1634, 1380, 1238, 1169, 1059 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 253.1804; found 253.1808.

3,5,5-Trimethyl-6-octanoyloxy-3,5,5-trimethylcyclohex-2-enone (7). Yellow oil (46 mg, 66%); ^1H NMR (400 MHz, CDCl_3) δ 5.89 (br s, 1H), 5.21 (s, 1H), 2.52 (d, $J = 18.4$ Hz, 1H), 2.45 (m, 2H), 2.16 (d, $J = 18.4$ Hz, 1H), 1.93 (s, 3H), 1.68 (tt, $J = 7.5, 7.4$ Hz, 2H), 1.31 (m, 8H), 1.07 (s, 3H), 0.97 (s, 3H), 0.86 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.3, 173.4, 159.3, 124.9, 80.3, 46.2, 37.8, 34.3, 31.8, 29.2, 29.1, 27.4, 25.2, 24.4, 22.7, 20.1, 14.2; IR (film) ν_{max} 2958, 2931, 2858, 1745, 1690, 1637, 1380, 1165, 1065 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{17}\text{H}_{29}\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 281.2117; found 281.2108.

6-Acetyloxy-3-methylcyclohex-2-enone (8). Yellow oil (30 mg, 71%); ^1H NMR (500 MHz, CDCl_3) δ 5.90 (br s, 1H), 5.29 (br s, 1H), 2.55 (m, 1H), 2.39 (br d, $J = 18.7$ Hz, 1H), 2.23 (m, 1H), 2.16 (s, 3H), 2.09 (m, 1H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.6,

170.4, 162.4, 125.5, 73.2, 30.5, 28.4, 24.3, 21.0; IR (film) ν_{\max} 2936, 1747, 1690, 1380, 1238, 1208, 1168 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_9\text{H}_{13}\text{O}_3$ $[\text{M} + \text{H}]^+$ 169.0865; found 169.0868.

6-Butanoyloxy-3-methylcyclohex-2-enone (9). Yellow oil (27 mg, 56%); ^1H NMR (500 MHz, CDCl_3) δ 5.90 (br s, 1H), 5.31 (dd, J = 13.3, 5.3 Hz, 1H), 2.55 (m, 1H), 2.40 (m, 3H), 2.22 (dddd, J = 7.8, 7.8, 5.2, 2.6 Hz, 1H), 2.09 (dddd, J = 17.1, 12.7, 12.7, 5.2 Hz, 1H), 1.97 (s, 3H), 1.70 (tq, J = 7.4, 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.7, 173.0, 162.3, 125.6, 72.9, 36.2, 30.6, 28.4, 24.3, 18.6, 13.7; IR (film) ν_{\max} 2966, 2936, 2876, 1743, 1689, 1633, 1381, 1177, 1104 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_3$ $[\text{M} + \text{H}]^+$ 197.1178; found 197.1178.

6-Hexanoyloxy-3-methylcyclohex-2-enone (10). Yellow oil (37 mg, 66%); ^1H NMR (400 MHz, CDCl_3) δ 5.89 (br s, 1H), 5.30 (dd, J = 13.3, 5.4 Hz, 1H), 2.55 (m, 1H), 2.40 (m, 3H), 2.21 (dddd, J = 7.8, 7.8, 5.2, 2.6 Hz, 1H), 2.08 (dddd, J = 16.9, 13.2, 11.7, 5.2 Hz, 1H), 1.96 (s, 3H), 1.66 (tt, J = 7.7, 7.7 Hz, 2H), 1.33 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.7, 173.2, 162.3, 125.6, 72.9, 34.3, 31.4, 30.5, 28.4, 24.7, 24.2, 22.4, 14.0; IR (film) ν_{\max} 2956, 2933, 2872, 1743, 1690, 1633, 1380, 1208, 1167, 1103 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{13}\text{H}_{21}\text{O}_3$ $[\text{M} + \text{H}]^+$ 225.1491; found 225.1505.

3-Methyl-6-octanoyloxycyclohex-2-enone (11). Yellow oil (47 mg, 74%); ^1H NMR (400 MHz, CDCl_3) δ 5.90 (br s, 1H), 5.31 (dd, J = 13.3, 5.4 Hz, 1H), 2.55 (m, 1H), 2.39 (m, 3H), 2.22 (dddd, J = 7.8, 7.8, 5.2, 2.6 Hz, 1H), 2.09 (dddd, J = 16.9, 11.8, 11.8, 5.2 Hz, 1H), 1.97 (s, 3H), 1.67 (tt, J = 7.1, 7.1 Hz, 2H), 1.31 (m, 8H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.7, 173.2, 162.3, 125.6, 72.9, 34.3, 31.8, 30.6, 29.2, 29.1, 28.4, 25.0, 24.3, 22.7, 14.2; IR (film) ν_{\max} 2930, 2856, 1743, 1691, 1633, 1380, 1162, 1105 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_3$ $[\text{M} + \text{H}]^+$ 253.1804; found 253.1797.

5-Acetyloxy-3-methyl-2-pentylcyclopent-2-enone (12). Yellow oil (45 mg, 81%); ^1H NMR (400 MHz, CDCl_3) δ 5.11 (dd, J = 6.9, 3.0 Hz, 1H), 2.97 (dd, J = 18.0, 6.9 Hz, 1H), 2.42 (br d, J = 18.0 Hz, 1H), 2.18 (m, 2H), 2.12 (s, 3H), 2.05 (s, 3H), 1.38 (m, 2H), 1.28 (m, 4H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 203.3, 170.8, 167.4, 139.6, 71.9, 38.9, 31.8, 28.0, 23.1, 22.6, 21.0, 17.3, 14.1; IR (film) ν_{\max} 2931, 2860, 1746, 1714, 1373, 1229, 1056 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{13}\text{H}_{21}\text{O}_3$ $[\text{M} + \text{H}]^+$ 225.1491; found 225.1513.

5-Butanoyloxy-3-methyl-2-pentylcyclopent-2-enone (13). Yellow oil (22 mg, 35%); ^1H NMR (500 MHz, CDCl_3) δ 5.12 (dd, J = 6.9, 3.0 Hz, 1H), 2.97 (dd, J = 18.0, 6.9 Hz, 1H), 2.36 (m, 3H), 2.18 (m, 2H), 2.05 (s, 3H), 1.67 (tq, J = 7.4, 7.1 Hz, 2H), 1.39 (tt, J = 7.8, 7.8 Hz, 2H), 1.27 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 203.3, 173.4, 167.2, 139.6, 71.8, 38.9, 36.0, 31.8, 28.0, 23.1, 22.6, 18.5, 17.3, 14.1, 13.7; IR (film) ν_{\max} 2959, 2932, 2874, 1743, 1714, 1643, 1388, 1174, 1055 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_3$ $[\text{M} + \text{H}]^+$ 253.1804; found 253.1844.

5-Hexanoyloxy-3-methyl-2-pentylcyclopent-2-enone (14). Yellow oil (52 mg, 74%); ^1H NMR (400 MHz, CDCl_3) δ 5.11 (dd, J = 6.9, 3.1 Hz, 1H), 2.96 (dd, J = 18.0, 6.9 Hz, 1H), 2.36 (m, 3H), 2.18 (m, 2H), 2.05 (s, 3H), 1.64 (tt, J = 7.5, 7.5 Hz, 2H), 1.38 (m, 2H), 1.27 (m, 8H), 0.88 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 203.3, 173.6, 167.1, 139.6, 71.8, 38.9, 34.2, 31.8, 31.4, 28.0, 24.7, 23.1, 22.6, 22.4, 17.3, 14.1, 14.0; IR (film) ν_{\max} 2956, 2931, 2859, 1743, 1715, 1643, 1388, 1164, 1112 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{17}\text{H}_{29}\text{O}_3$ $[\text{M} + \text{H}]^+$ 281.2117; found 281.2126.

3-Methyl-5-octanoyloxy-2-pentylcyclopent-2-enone (15). Yellow oil (42 mg, 54%); ^1H NMR (500 MHz, CDCl_3) δ 5.11 (dd, J = 6.9, 3.0 Hz, 1H), 2.96 (dd, J = 18.0, 6.9 Hz, 1H), 2.36 (m, 3H), 2.18 (m, 2H), 2.04 (s, 3H), 1.63 (tt, J = 7.8, 7.8 Hz, 2H), 1.38 (tt, J = 7.6, 7.6 Hz, 2H), 1.26 (m, 12H), 0.86 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 203.3, 173.6, 167.1, 139.6, 71.7, 38.9, 34.2, 31.8, 31.7, 29.2, 29.0, 28.0, 25.0, 23.1, 22.7, 22.6, 17.3, 14.2, 14.1; IR (film) ν_{\max} 2956, 2929, 2858, 1745, 1716, 1645, 1387, 1162, 1110 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{19}\text{H}_{33}\text{O}_3$ $[\text{M} + \text{H}]^+$ 309.2430; found 309.2458.

6-Acetyloxy-3-ethoxycyclohex-2-enone (16). Yellow oil (29 mg, 59%); ^1H NMR (400 MHz, CDCl_3) δ 5.36 (s, 1H), 5.28 (dd, J = 12.6, 5.2 Hz, 1H), 3.90 (m, 2H), 2.64 (ddd, J = 17.1, 12.0, 5.1 Hz, 1H), 2.49 (ddd, J = 17.8, 5.3, 2.9 Hz, 1H), 2.21 (dddd, J = 10.4, 5.2, 4.6, 3.0 Hz, 1H), 2.16 (s, 3H), 2.08 (dddd, J = 17.6, 12.5, 12.5, 5.3 Hz, 1H), 1.36 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.3, 176.8, 170.5, 101.4, 72.6, 65.0, 28.1, 26.9, 21.1, 14.2; IR (film) ν_{\max} 2984, 1741, 1673, 1602, 1378, 1236, 1191, 1046 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{10}\text{H}_{15}\text{O}_4$ $[\text{M} + \text{H}]^+$ 199.0970; found 199.0986.

6-Butanoyloxy-3-ethoxycyclohex-2-enone (17). Yellow oil (48 mg, 85%); ^1H NMR (400 MHz, CDCl_3) δ 5.33 (s, 1H), 5.27 (dd, J = 12.5, 5.3 Hz, 1H), 3.88 (m, 2H), 2.63 (ddd, J = 17.4, 11.9, 5.2 Hz, 1H), 2.47 (ddd, J = 17.8, 5.3, 3.2 Hz, 1H), 2.37 (m, 2H), 2.18 (dddd, J = 8.3, 8.3, 5.2, 3.0 Hz, 1H), 2.06 (dddd, J = 17.7, 12.4, 12.4, 5.3 Hz, 1H), 1.68 (tq, J = 7.4, 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.3, 176.6, 173.0, 101.4, 72.3, 64.9, 36.1, 28.1, 26.9, 18.5, 14.1, 13.7; IR (film) ν_{\max} 2966, 2940, 2877, 1743, 1678, 1605, 1380, 1187, 1101 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{12}\text{H}_{19}\text{O}_4$ $[\text{M} + \text{H}]^+$ 227.1283; found 227.1295.

3-Ethoxy-6-hexanoyloxycyclohex-2-enone (18). Yellow oil (51 mg, 81%); ^1H NMR (500 MHz, CDCl_3) δ 5.35 (s, 1H), 5.27 (dd, J = 12.6, 5.2 Hz, 1H), 3.89 (m, 2H), 2.63 (ddd, J = 17.5, 12.0, 5.1 Hz, 1H), 2.48 (ddd, J = 17.8, 5.2, 2.9 Hz, 1H), 2.39 (m, 2H), 2.19 (dddd, J = 8.2, 8.2, 5.2, 3.0 Hz, 1H), 2.07 (dddd, J = 17.8, 12.5, 12.5, 5.3 Hz, 1H), 1.66 (tt, J = 7.6, 7.6 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.31 (m, 4H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.3, 176.7, 173.2, 101.4, 72.3, 65.0, 34.3, 31.3, 28.1, 26.9, 24.7, 22.4, 14.2, 14.0; IR (film) ν_{\max} 2954, 2933, 2872, 1744, 1667, 1604, 1379, 1196, 1169 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{14}\text{H}_{23}\text{O}_4$ $[\text{M} + \text{H}]^+$ 255.1596; found 255.1596.

3-Ethoxy-6-octanoyloxycyclohex-2-enone (19). Yellow oil (61 mg, 86%); ^1H NMR (400 MHz, CDCl_3) δ 5.35 (s, 1H), 5.27 (dd, J = 12.5, 5.2 Hz, 1H), 3.88 (m, 2H), 2.63 (ddd, J = 17.4, 11.9, 5.0 Hz, 1H), 2.48 (ddd, J = 17.6, 5.1, 2.8 Hz, 1H), 2.40 (m, 2H), 2.19 (dddd, J = 8.3, 8.3, 5.2, 3.0 Hz, 1H), 2.07 (dddd, J = 17.8, 12.3, 12.3, 5.3 Hz, 1H), 1.65 (tt, J = 7.2, 7.4 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H), 1.28 (m, 8H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.3, 176.7, 173.2, 101.4, 72.3, 64.9, 34.3, 31.7, 29.1, 29.0, 28.1, 26.9, 25.0, 22.7, 14.2, 14.1; IR (film) ν_{\max} 2951, 2917, 2852, 1744, 1661, 1605, 1470, 1170, 872 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{16}\text{H}_{27}\text{O}_4$ $[\text{M} + \text{H}]^+$ 283.1909; found 283.1925.

(3S,3aS,6R,6aS,7R,9bS)-7-Acetyloxy-3,6,9-trimethyl-2,8-dioxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno[4,5-b]furan-6-yl Acetate (26). White amorphous solid (55 mg, 60%); $[\alpha]_{\text{D}}^{20} +45.33$ (c 1.16, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 5.13 (d, J = 3.4 Hz, 1H), 4.83 (br d, J = 11.0 Hz, 1H), 4.05 (br s, 1H), 2.60 (ddd, J = 18.1, 13.6, 4.4 Hz, 1H), 2.28 (m, 3H), 2.14 (m, 1H), 2.09 (s, 3H), 2.06 (m, 1H), 1.95 (s, 3H), 1.95 (s, 3H), 1.46 (dddd, J = 14.8, 13.6, 11.3, 3.7 Hz, 1H), 1.27 (d, J = 6.9 Hz, 3H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 201.1, 176.7, 170.5, 169.8, 157.7, 140.6, 84.7, 81.1, 73.7, 52.5, 48.6, 41.3, 37.9, 25.7, 22.6, 20.8, 20.7, 12.6, 10.1; IR (film) ν_{\max} 2931, 1784, 1728, 1235, 1017, 753 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{19}\text{H}_{25}\text{O}_7$ $[\text{M} + \text{H}]^+$ 365.1600; found 365.1612.

(3S,3aS,6R,6aS,7R,9bS)-7-Butanoyloxy-3,6,9-trimethyl-2,8-dioxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno[4,5-b]furan-6-yl Acetate (27). White amorphous solid (60 mg, 61%); $[\alpha]_{\text{D}}^{20} +90.95$ (c 2.86, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.11 (d, J = 3.2 Hz, 1H), 4.82 (br d, J = 11.0 Hz, 1H), 4.04 (br s, 1H), 2.59 (ddd, J = 18.0, 13.6, 4.4 Hz, 1H), 2.30 (m, 3H), 2.23 (t, J = 3.6 Hz, 1H), 2.15 (m, 1H), 2.06 (m, 1H), 1.94 (s, 3H), 1.93 (s, 3H), 1.64 (tq, J = 7.5, 7.5 Hz, 2H), 1.45 (dddd, J = 14.6, 14.6, 11.2, 3.6 Hz, 1H), 1.25 (d, J = 6.9 Hz, 3H), 1.23 (s, 3H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 176.7, 172.5, 170.5, 157.8, 140.6, 84.6, 81.1, 73.6, 52.5, 48.5, 41.3, 37.9, 35.7, 25.6, 22.6, 20.8, 18.3, 13.7, 12.6, 10.1; IR (film) ν_{\max} 2967, 2876, 1785, 1724, 1250, 1171, 997 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{21}\text{H}_{29}\text{O}_7$ $[\text{M} + \text{H}]^+$ 393.1913; found 393.1904.

(3S,3aS,6R,6aS,7R,9bS)-7-Hexanoyloxy-3,6,9-trimethyl-2,8-dioxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno[4,5-b]furan-6-yl Acetate (28). White amorphous solid (67 mg, 64%); $[\alpha]_{\text{D}}^{20} +50.97$ (c 0.42, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.10 (d, J = 3.1 Hz,

1H), 4.82 (br d, $J = 11.0$ Hz, 1H), 4.05 (br s, 1H), 2.60 (ddd, $J = 18.0$, 13.6, 4.4 Hz, 1H), 2.31 (m, 3H), 2.25 (m, 1H), 2.15 (m, 1H), 2.06 (m, 1H), 1.94 (s, 3H), 1.93 (s, 3H), 1.61 (tt, $J = 7.1$, 7.1 Hz, 2H), 1.45 (dddd, $J = 14.6$, 14.6, 11.2, 3.6 Hz, 1H), 1.31 (m, 4H), 1.25 (d, $J = 6.9$ Hz, 3H), 1.23 (s, 3H), 0.87 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 176.7, 172.6, 170.5, 157.7, 140.6, 84.6, 81.1, 73.6, 52.5, 48.5, 41.3, 37.9, 33.8, 31.2, 25.7, 24.4, 22.6, 22.4, 20.9, 14.0, 12.6, 10.1; IR (film) ν_{max} 2935, 2873, 1787, 1727, 1249, 1170, 998 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{23}\text{H}_{33}\text{O}_7$ $[\text{M} + \text{H}]^+$ 421.2226; found 421.2214.

(3S,3aS,6R,6aS,7R,9bS)-3,6,9-Trimethyl-7-octanoyloxy-2,8-dioxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno[4,5-b]furan-6-yl Acetate (29). White amorphous solid (80 mg, 71%); $[\alpha]_{\text{D}}^{20} +44.34$ (c 0.99, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 5.13 (d, $J = 3.3$ Hz, 1H), 4.82 (br d, $J = 11.2$ Hz, 1H), 4.06 (br s, 1H), 2.61 (ddd, $J = 18.1$, 13.6, 4.4 Hz, 1H), 2.34 (m, 3H), 2.29 (m, 1H), 2.25 (m, 1H), 2.15 (m, 1H), 2.08 (m, 1H), 1.96 (s, 6H), 1.62 (tt, $J = 7.1$, 7.1 Hz, 2H), 1.46 (dddd, $J = 14.7$, 14.7, 11.2, 3.6 Hz, 1H), 1.32 (m, 8H), 1.28 (d, $J = 6.9$ Hz, 3H), 1.24 (s, 3H), 0.87 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 201.2, 176.8, 172.7, 170.5, 157.7, 140.7, 84.7, 81.2, 73.6, 52.6, 48.6, 41.4, 37.9, 33.9, 31.8, 29.1, 29.1, 25.7, 24.8, 22.7, 22.6, 20.9, 14.2, 12.6, 10.1; IR (film) ν_{max} 2929, 2859, 1785, 1734, 1728, 1233, 1093, 1016 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{25}\text{H}_{37}\text{O}_7$ $[\text{M} + \text{H}]^+$ 449.2539; found 449.2575.

(3S,3aR,4S)-3-Acetyloxy-7-((S)-1-((tert-butyldimethylsilyl)oxy)-2-hydroxypropan-2-yl)-1,4-dimethyl-2-oxo-2,3,3a,4,5,6-hexahydroazulen-4-yl Acetate (30). Yellow oil (118 mg, 98%); $[\alpha]_{\text{D}}^{20} -79.09$ (c 1.77, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 6.80 (br s, 1H), 5.30 (d, $J = 2.9$ Hz, 1H), 4.17 (br s, 1H), 3.67 (d, $J = 9.7$ Hz, 1H), 3.50 (d, $J = 9.7$ Hz, 1H), 2.89 (m, 1H), 2.55 (ddd, $J = 14.7$, 6.4, 3.4 Hz, 1H), 2.23 (ddd, $J = 16.4$, 6.5, 3.2 Hz, 1H), 2.14 (ddd, $J = 14.1$, 2.9, 2.7 Hz, 1H), 2.10 (s, 3H), 1.97 (s, 3H), 1.81 (d, $J = 2.1$ Hz, 3H), 1.29 (s, 3H), 1.24 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 202.3, 170.8, 169.8, 161.1, 157.1, 135.7, 119.2, 83.0, 76.4, 73.3, 68.5, 51.8, 40.2, 25.9, 25.1, 23.9, 22.8, 22.4, 20.9, 18.3, 8.5, -5.3; IR (film) ν_{max} 3447, 2930, 1749, 1707, 1626, 1246, 1093, 837 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{25}\text{H}_{41}\text{O}_7\text{Si}$ $[\text{M} + \text{H}]^+$ 481.2622; found 481.2610.

(3S,3aR,4S)-3-Butanoyloxy-7-((S)-1-((tert-butyldimethylsilyl)oxy)-2-hydroxypropan-2-yl)-1,4-dimethyl-2-oxo-2,3,3a,4,5,6-hexahydroazulen-4-yl Acetate (31). Yellow oil (71 mg, 56%); $[\alpha]_{\text{D}}^{20} -75.79$ (c 2.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.80 (br s, 1H), 5.30 (d, $J = 2.8$ Hz, 1H), 4.17 (br s, 1H), 3.67 (d, $J = 9.7$ Hz, 1H), 3.50 (d, $J = 9.7$ Hz, 1H), 2.90 (m, 1H), 2.54 (ddd, $J = 14.6$, 6.4, 3.4 Hz, 1H), 2.32 (m, 2H), 2.22 (ddd, $J = 16.8$, 6.4, 3.2 Hz, 1H), 2.11 (ddd, $J = 14.7$, 11.7, 3.1 Hz, 1H), 1.96 (s, 3H), 1.81 (d, $J = 2.6$ Hz, 3H), 1.67 (tq, $J = 7.4$, 7.4 Hz, 2H), 1.28 (s, 3H), 1.24 (s, 3H), 0.97 (t, $J = 7.4$ Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.4, 172.5, 170.8, 161.1, 157.1, 135.7, 119.2, 83.0, 76.4, 73.1, 68.5, 51.8, 40.2, 36.0, 25.9, 25.1, 24.0, 22.8, 22.4, 18.5, 18.3, 13.8, 8.5, -5.3; IR (film) ν_{max} 3496, 2960, 2932, 2858, 1743, 1705, 1626, 1249, 1092, 836 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{27}\text{H}_{44}\text{O}_7\text{Si}$ $[\text{M}]^+$ 508.2856; found 508.2859.

(3S,3aR,4S)-3-Hexanoyloxy-7-((S)-1-((tert-butyldimethylsilyl)oxy)-2-hydroxypropan-2-yl)-1,4-dimethyl-2-oxo-2,3,3a,4,5,6-hexahydroazulen-4-yl Acetate (32). Yellow oil (101 mg, 75%); $[\alpha]_{\text{D}}^{20} -88.73$ (c 2.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.79 (br s, 1H), 5.28 (d, $J = 2.8$ Hz, 1H), 4.16 (br s, 1H), 3.66 (d, $J = 9.7$ Hz, 1H), 3.49 (d, $J = 9.7$ Hz, 1H), 2.89 (m, 1H), 2.54 (ddd, $J = 14.5$, 6.2, 3.2 Hz, 1H), 2.32 (m, 2H), 2.22 (ddd, $J = 16.3$, 6.4, 3.0 Hz, 1H), 2.11 (ddd, $J = 16.5$, 11.6, 3.1 Hz, 1H), 1.95 (s, 3H), 1.81 (d, $J = 2.3$ Hz, 3H), 1.63 (m, 2H), 1.32 (m, 4H), 1.28 (s, 3H), 1.23 (s, 3H), 0.87 (m, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.4, 172.7, 170.8, 161.1, 157.1, 135.7, 119.2, 83.0, 76.4, 73.1, 68.5, 51.8, 40.2, 34.1, 31.3, 25.9, 25.1, 24.6, 23.9, 22.8, 22.4, 22.4, 18.3, 14.0, 8.5, -5.3; IR (film) ν_{max} 3488, 2956, 2932, 2860, 1743, 1707, 1625, 1246, 1092, 838 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{29}\text{H}_{49}\text{O}_7\text{Si}$ $[\text{M} + \text{H}]^+$ 537.3248; found 537.3253.

(3S,3aR,4S)-7-((S)-1-((tert-Butyldimethylsilyl)oxy)-2-hydroxypropan-2-yl)-1,4-dimethyl-3-octanoyloxy-2-oxo-2,3,3a,4,5,6-hexahydroazulen-4-yl Acetate (33). Yellow oil (128 mg, 91%);

$[\alpha]_{\text{D}}^{20} -91.91$ (c 1.53, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 6.80 (br s, 1H), 5.30 (d, $J = 2.8$ Hz, 1H), 4.16 (br s, 1H), 3.67 (d, $J = 9.7$ Hz, 1H), 3.50 (d, $J = 9.7$ Hz, 1H), 2.90 (m, 1H), 2.54 (ddd, $J = 14.7$, 6.5, 3.4 Hz, 1H), 2.34 (m, 2H), 2.23 (ddd, $J = 16.3$, 6.5, 3.2 Hz, 1H), 2.12 (ddd, $J = 14.7$, 11.6, 3.1 Hz, 1H), 1.96 (s, 3H), 1.82 (d, $J = 2.1$ Hz, 3H), 1.63 (m, 2H), 1.32 (m, 4H), 1.29 (s, 3H), 1.27 (m, 4H), 1.24 (s, 3H), 0.88 (m, 12H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 202.4, 172.7, 170.8, 161.1, 157.1, 135.8, 119.2, 83.0, 76.4, 73.1, 68.5, 51.8, 40.2, 34.2, 31.8, 29.2, 29.1, 25.9, 25.1, 25.0, 24.0, 22.8, 22.7, 22.5, 18.3, 14.2, 8.5, -5.3; IR (film) ν_{max} 3467, 2930, 2859, 1740, 1706, 1624, 1248, 1092, 836 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{31}\text{H}_{53}\text{O}_7\text{Si}$ $[\text{M} + \text{H}]^+$ 565.3561; found 565.3549.

For the preparation of **36**, a larger scale experiment was run for the synthesis of **33**: To a suspension of KMnO_4 (746 mg, 4.720 mmol, 2.10 equiv) in dry benzene (50 mL) at 85 °C were added octanoic acid (78.68 mmol, 12.5 mL, 35.0 equiv) and its anhydride (21.36 mmol, 6.3 mL, 9.50 equiv). The mixture was vigorously stirred until the suspension changed from purple to brown (30 min), and then, **25** (950 mg, 2.248 mmol) was added (dissolved in the minimum amount of dry benzene). The reaction was heated overnight at 85 °C. It is very important to keep a vigorous stirring of the reaction. Then, the mixture was cooled to room temperature and filtered through an Al_2O_3 /Celite pad rinsing with EtOAc. The solvent was evaporated under reduced pressure, and the crude oil was purified by flash column chromatography (gradient eluent from 0 to 20% EtOAc/hexanes) to lead to compound **33** (1.09 g, 86% yield).

(3S,3aS,6R,6aR,9bS)-3,6,9-Trimethyl-2,8-dioxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno[4,5-b]furan-6-yl Acetate (21). A solution of α -santonin **20** (500 mg, 2.03 mmol) in acetic acid (200 mL) was irradiated in a quartz Hanovia reactor equipped with a Hg medium pressure lamp for 5 h. Removal of the solvent under vacuum and purification of the crude mixture by flash column chromatography (40% EtOAc/hexanes) afforded *O*-acetylphotosantonic lactone **21** as a white solid (230 mg, 38% yield). Spectroscopic data were in accordance with literature reported values.¹²

(3aS,4S)-7-((S)-1,2-Dihydroxypropan-2-yl)-1,4-dimethyl-2-oxo-2,3,3a,4,5,6-hexahydroazulen-4-yl Acetate (24). A solution of compound **23**¹³ (570 mg, 2.30 mmol) in acetic acid (200 mL) was irradiated and stirred in a quartz Hanovia reactor equipped with a Hg medium pressure lamp for 2 h. Removal of the solvent under vacuum and purification of the crude mixture by flash column chromatography (75% EtOAc/hexanes) afforded the product **24** as a colorless oil (510 mg, 72% yield). Spectroscopic data were in accordance with literature reported values.¹³

(3aS,4S)-7-((S)-1-((tert-Butyldimethylsilyl)oxy)-2-hydroxypropan-2-yl)-1,4-dimethyl-2-oxo-2,3,3a,4,5,6-hexahydroazulen-4-yl Acetate (25). Compound **24** (500 mg, 1.62 mmol) was dissolved in dry THF (11 mL), and imidazole (330 mg, 4.86 mmol, 3.00 equiv) was added. The reaction mixture was cooled to 0 °C, and a solution of TBDMSCl (366 mg, 2.43 mmol, 1.50 equiv) in dry THF (5 mL) was added dropwise. The reaction was stirred for 3 h until completion according to TLC analysis. The reaction was treated with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 \times 15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 , and the solvent was evaporated under reduced pressure. Purification by flash column chromatography (30% EtOAc/hexanes) afforded **25** as a yellow oil (678 mg, 99% yield): $[\alpha]_{\text{D}}^{20} +28.19$ (c 1.73, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 6.77 (s, 1H), 4.14 (br s, 1H), 3.68 (d, $J = 9.6$ Hz, 1H), 3.49 (d, $J = 9.7$ Hz, 1H), 2.93 (m, 1H), 2.59 (ddd, $J = 15.1$, 6.9, 2.7 Hz, 1H), 2.42 (dd, $J = 19.1$, 2.6 Hz, 1H), 2.37 (dd, $J = 19.2$, 2.6 Hz, 1H), 2.23 (ddd, $J = 17.1$, 6.8, 2.5 Hz, 1H), 2.00 (s, 3H), 1.94 (ddd, $J = 14.8$, 11.9, 2.7 Hz, 1H), 1.78 (d, $J = 1.8$ Hz, 3H), 1.28 (s, 3H), 1.13 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 208.5, 170.7, 163.5, 156.9, 137.7, 119.6, 84.7, 76.3, 68.5, 45.9, 40.1, 37.3, 25.9, 25.1, 22.9, 22.6, 22.4, 18.3, 8.4, -5.3; IR (film) ν_{max} 3457, 2930, 2857, 1732, 1694, 1627, 1464, 1368, 1250, 1093, 837 cm^{-1} ; HRMS (APGC) calcd. for $\text{C}_{23}\text{H}_{39}\text{O}_5\text{Si}$ $[\text{M} + \text{H}]^+$ 423.2567; found 423.2587.

(1S,8S,8aR)-8-Acetoxy-5-((S)-1,2-dihydroxypropan-2-yl)-3,8-dimethyl-2-oxo-1,2,6,7,8,8a-hexahydroazulen-1-yl Octanoate

(34). To a solution of compound **33** (163 mg, 0.288 mmol) in dry THF (2 mL) at 0 °C was added TBAF (1 M solution in THF, 0.575 mL, 0.575 mmol, 2.00 equiv) dropwise. The mixture was stirred at room temperature until completion according to TLC analysis (2 h). The reaction was treated with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 \times 5 mL). Combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 , and the solvent was removed under vacuum. Purification by flash column chromatography (70% EtOAc/hexanes) afforded product **34** as a yellow oil (74 mg, 61% yield): $[\alpha]_{\text{D}}^{20}$ -92.32 (*c* 1.92, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 6.87 (s, 1H), 5.25 (d, *J* = 2.8 Hz, 1H), 4.22 (br s, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.52 (d, *J* = 11.0 Hz, 1H), 2.94 (m, 1H), 2.80 (br s, OH), 2.57 (ddd, *J* = 14.8, 6.4, 3.4 Hz, 1H), 2.33 (m, 2H), 2.21 (ddd, *J* = 16.4, 6.4, 3.2 Hz, 1H), 2.11 (ddd, *J* = 14.8, 11.7, 3.1 Hz, 1H), 1.96 (s, 3H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.62 (tt, *J* = 7.4, 7.4 Hz, 2H), 1.34 (s, 3H), 1.28 (m, 8H), 1.24 (s, 3H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 202.6, 172.8, 170.8, 160.9, 156.8, 136.0, 119.6, 83.0, 77.4, 73.3, 68.1, 51.7, 40.3, 34.1, 31.8, 29.2, 29.1, 25.2, 24.9, 24.1, 23.0, 22.7, 22.5, 14.2, 8.6; IR (film) ν_{max} 3449, 2931, 2858, 1739, 1704, 1623, 1370, 1244, 1163, 1045 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{37}\text{O}_7$ $[\text{M} - \text{H}]^-$ 449.2539; found 449.2539.

(35, **3aR,6S,6aR,7S,9bS**)-6-Acetoxy-3,3a-dihydroxy-3,6,9-trimethyl-2,8-dioxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno-[4,5-*b*]furan-7-yl Octanoate (**36**). Guaianediol **34** (70 mg, 0.155 mmol) was dissolved in a 20:2.5:1 acetone/*t*BuOH/ H_2O solution (8 mL, conc. 0.02 M) and then cooled at 0 °C. MeSO_2NH_2 (18 mg, 0.186 mmol, 1.20 equiv), NMO (22 mg, 0.186 mmol, 1.20 equiv), and OsO_4 (2 mg, 0.008 mmol, 0.05 equiv) were added. The reaction was stirred for 24 h at room temperature and then treated with saturated aqueous Na_2SO_3 solution (5 mL). After stirring for 40 min, water (5 mL) was added and the mixture was extracted with EtOAc (4 \times 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , and the solvent was removed under reduced pressure. This material (75 mg) was used without further purification in the subsequent step. Crude compound **35** (ca. 75 mg, 0.155 mmol) was dissolved in a 1.3:1 MeCN/pH 7 buffer solution mixture (15 mL). TEMPO (13 mg, 0.078 mmol, 0.50 equiv), NaClO_2 (0.224 mL, 0.620 mmol, 4.00 equiv, 25% w/w in H_2O), and NaClO (0.04 mL) were added. The mixture was stirred at room temperature for 4 h, and then aqueous saturated Na_2SO_3 solution (4 mL) was added. The pH was set to 3 by adding aqueous 2 N HCl solution. The mixture was extracted with EtOAc (4 \times 10 mL) and washed with brine (15 mL). After drying over anhydrous Na_2SO_4 , the solvent was removed under reduced pressure, affording pure compound **36** as a white amorphous solid (48 mg, 65%): $[\alpha]_{\text{D}}^{20}$ -166.5 (*c* 0.30, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 5.44 (br s, 1H), 5.14 (d, *J* = 3.6 Hz, 1H), 4.34 (br s, 1H), 2.78 (m, 1H), 2.59 (br s, OH), 2.34 (m, 2H), 2.25 (ddd, *J* = 13.7, 3.9, 3.9 Hz, 1H), 2.01 (m, 1H), 1.97 (d, *J* = 2.5 Hz, 3H), 1.95 (s, 3H), 1.88 (ddd, *J* = 15.6, 4.2, 4.2 Hz, 1H), 1.63 (m, 4H), 1.44 (s, 3H), 1.31 (s, 3H), 1.27 (m, 6H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.4, 175.6, 172.8, 170.6, 156.2, 141.7, 84.7, 82.5, 80.1, 77.8, 73.8, 52.7, 34.0, 31.8, 31.7, 29.1, 29.0, 24.9, 24.6, 22.8, 22.7, 19.9, 15.9, 14.2, 10.2; IR (film) ν_{max} 3438, 2957, 2928, 2858, 1794, 1727, 1369, 1260, 1095, 1018, 804 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{35}\text{O}_9$ $[\text{M} - \text{H}]^-$ 479.2281; found 479.2287.

■ ASSOCIATED CONTENT

■ Supporting Information

Spectroscopic data for all 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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