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Exploiting the Facile Release of Trifluoroacetate for the α-Methylenation of the Sterically Hindered Carbonyl Groups on (+)-Sclareolide and (−)-Eburnamonine

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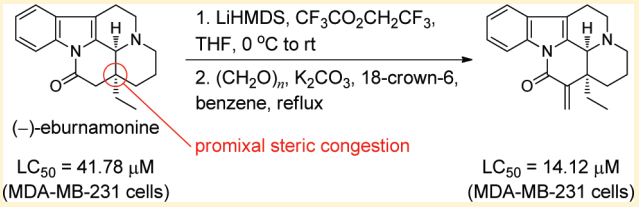
Supporting Information

ABSTRACT: An efficient method for the α-methylenation of carbonyl groups is reported, and this transformation is accomplished by a facile elimination of trifluoroacetate during the formation of the olefin. This method represents an improvement beyond existing protocol in cases of steric hindrance, and we have demonstrated the utility of the process across a series of ketones, lactams, and lactones. Additionally, we have applied this method to produce semisynthetic derivatives of the natural products (+)-sclareolide and (−)-eburnamonine, in which the carbonyl group is proximal to bulky functional groups. Mechanistic insight is also provided from a time course of ^{19}F NMR. Biological evaluation of the natural-product-derived enones led to the identification of a derivative of (−)-eburnamonine with significant cytotoxicity (LC_{50} = 14.12 μM) in drug-resistant MDA-MB-231 breast cancer cells.



INTRODUCTION

Molecules, especially natural products, with electrophilic functional groups that can covalently bind to nucleophiles are valuable biological probes.[1−4] Typical examples of these electrophilic groups are α,β-unsaturated carbonyl groups and epoxides.[2,3] One of the most prominent types of α,β-unsaturated carbonyl groups in natural products is the α-methylene-γ-lactone, as nearly 3% of the known natural products contain this feature.[5,6] A representative class of natural products that commonly have the α-methylene-γ-lactone is the sesquiterpene lactones, and some examples of members are parthenolide (**1**) and helenalin (**2**) (Figure 1). (+)-Sclareolide (**3**) is another member of the sesquiterpene lactone family of natural products that has a γ-lactone, but no α-methylene group is present.

Sclareolide is a widely used as a building block in many synthetic strategies because of its availability, but the natural product itself is not biologically active.[7−12] We hypothesized that incorporating an α-methylene group onto the existing carbonyl group may generate new biological activity and that such a synthetic and biological objective may have significant applications to other natural products. However, our efforts to extend this methodology to **3** and construct the α-methylene next to the carbonyl group proved to be quite troublesome, presumably due to adjacent steric congestion from the flanking axial methyl groups. Thus, efficiently accessing derivatives of sclareolide became a challenge, yet modifying a carbonyl group on other natural products would likely present a similar problem. To overcome this synthetic obstacle, we have developed an efficient and high-yielding method for the α-methylenation of carbonyl groups using a facile release of trifluoroacetate. This olefination strategy avoids the use of traditional phosphorus groups that are incompatible when bulky groups are present and was readily applied to other carbonyl-containing compounds and natural products. In addition to installing the α-methylene to (+)-sclareolide by trifluoroacetate release, an α-methylene group was incorporated next to the carbonyl group of the alkaloid, (−)-eburnamonine, and this synthetic derivative showed potent biological activity in drug-resistant MDA-MB-231 breast cancer cells.

RESULTS AND DISCUSSION

Methods to install an α-methylene functional group on a γ-butyrolactone are well-known,[13−18] and representative examples are an Eschenmoser methenylation,[13] the Horner−Wadsworth−Emmons approach of Wiemer,[14] a deformylative olefination,[15] and a deacetylative olefination.[17] We initiated our studies with the application of the former two methods to (+)-sclareolide (**3**), and unreacted starting material was returned almost exclusively. However, the application of Wiemer's protocol[14b] to **3** gave a minor, crystalline byproduct **4**, which in turn provided the first X-ray crystal structure of the skeleton of (+)-sclareolide (Scheme 1). The highly congested nature across the ring system is apparent, due to the positioning of the three axial methyl groups. Thus, we abandoned other olefination protocols that would require the attachment of a bulky group at the carbon adjacent to the carbonyl group in **3**, such as the preparation of a precursor for a Wittig reaction,[16] and focused our attention on olefination by formyl group release.[15] Our reactions using the deformylative olefination with **3** were somewhat successful and provided

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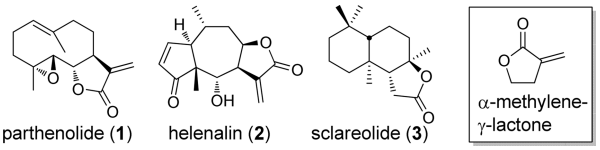
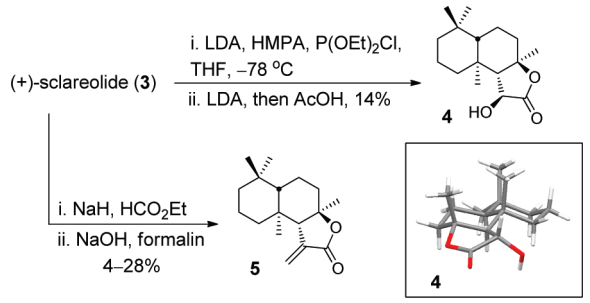


Figure 1. Sesquiterpene lactone natural products and the α-methylene-γ-lactone group.

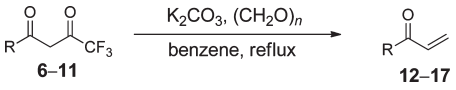
Scheme 1



the desired olefin **5**, albeit in low yields (i.e., 4−28%) and despite considerable attempts at optimization (see Scheme 1).

Three variants to the formyl group release protocol have been reported to install olefins at the α-position of carbonyl groups: deacetylative,[17] decarboxylative,[18] and deoxalative methylenations.[19] The decarboxylative methylenations developed by Grieco[18a] and Johnson[18b] are attractive due to the *in situ* release of carbon dioxide. Unfortunately, the installation of a carboxylate at the α-position of a carbonyl group can be difficult, and the resulting intermediate can also be unstable. Deformylative methylenations[15] are the ready alternative due to stability of the intermediate formyl group, but the release of formate is not a facile process. Using inspiration from literature precedent of Danheiser and co-workers who described the benefits of releasing trifluoroacetate rather than formate,[20] we decided to exchange the formyl group with a trifluoroacetyl group. Indeed, the release of trifluoroacetate has been rarely examined in synthesis.[20,21] We hypothesized that this modification would dramatically enhance the utility of the α-methylenation process and extend beyond the scope of the pioneering deacetylative work of Ueno and co-workers,[17] because each of the protons is exchanged with fluorine. To determine the potential of the α-methylenation from trifluoroacetate release, we required a series of substrates that contain a 4,4,4-trifluoromethyl-1,3-butanedione functional group. These systems are known to exist more favorably in the enol tautomer (eq 1),[22] and the enolic proton is highly acidic (a typical pK_a = 8−9).[23] We envisioned that the use of these substrates with a trifluoromethyl group would not only require a milder base to promote addition to formaldehyde (due to the enhanced acidity of the enolic proton), but also it would be more prone to elimination, following addition, and form the desired olefin. We examined 4,4,4-trifluoromethyl-1,3-butanedione-containing substrates **6**−**11** and found that each converted to the respective olefin **12**−**17** in excellent yields using K_2CO_3 with paraformaldehyde in refluxing benzene (Table 1). Although during our optimizations we found that other bases promote the process, K_2CO_3 routinely provided superior conversions and was also easily removed by aqueous workup. The mild reaction conditions of this olefination strategy through trifluoroacetate release are critical to the high isolated yields, because enones are quite sensitive, and for

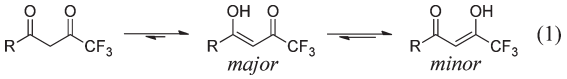
Table 1. Olefination by Trifluoroacetate Release



entry	starting material	product	yield[a]
1	**6**	**12**	93%
2	**7**	**13**	83%
3	**8**	**14**	76%
4	**9**	**15**	98%
5	**10**	**16**	61%[b]
6	**11**	**17**	95%[b]

[a] All yields refer to isolated, pure products. [b] The additive 18-crown-6 was used.

example, homopolymerization of α-aryl vinyl ketones is known.[24] Furthermore, this strategy avoids the use of toxic selenium reagents, which are a common choice for synthesizing vinyl ketones, such as compound **12**.[25] Additionally, the vinyl naphthyl ketone **14** is highly reactive and methods to prepare **14** require the use of harsh oxidants, such as chromium, or are low-yielding.[26] In the case of the nonaromatic substrates, we found that the camphor derivative **11** required the additive 18-crown-6 to achieve 95% conversion to product **17**. With these data about the efficient conversion of 4,4,4-trifluoromethyl-1,3-butanedione-containing substrates to olefins, we proceeded to more complex substrates and natural products that provide a requisite carbonyl group.



The next step to implement our strategy was the α-trifluoroacetylation of carbonyl groups of substrates **18**−**26** that encompass an array of ketones, lactams, and lactones (Table 2). We resorted to Danheiser's protocol for an efficient trifluoroacetylation with LiHMDS and $CF_3CO_2CH_2CF_3$.[20] In the cases of the ketone substrates **18**−**22**, we found that nearly quantitative conversions were routinely obtained after warming the reaction mixture from 0 °C to rt rather than performing the reaction at −78 °C. However, in the cases of the lactam **24** and lactones **25** and **26**, *O*-trifluoroacetylation was a potential concern at 0 °C, so these reactions were conducted at −78 °C. Next, we immediately subjected the unpurified trifluoroacetylated intermediates from substrates **18**−**26** to olefination by

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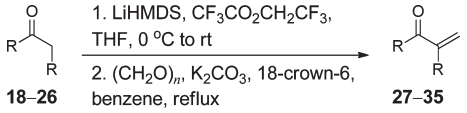
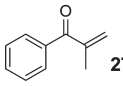
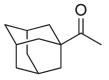
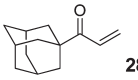
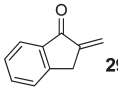
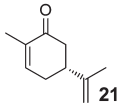
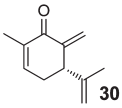
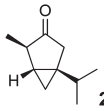
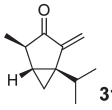
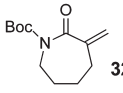
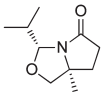
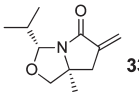
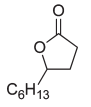
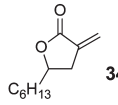
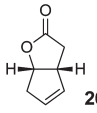
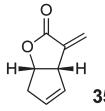
Table 2. Scope of Two-Step Conversion of Carbonyl Groups to Enones by Trifluoroacetate Release



18–26 27–35

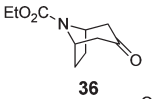
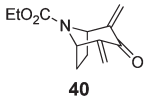
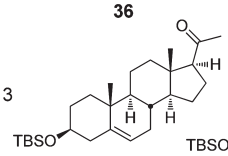
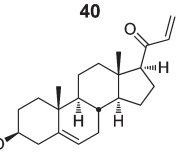
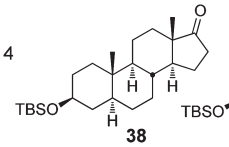
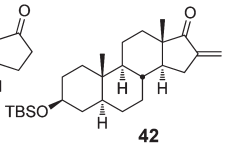
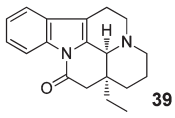
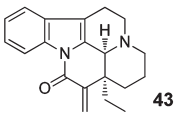
entry	starting material	product	yield[a]
1	 18	 27	92%
2	 19	 28	88%
3	 20	 29	98%
4	 21	 30	85%
5	 22	 31	82%
6	 23	 32	83%
7	 24	 33	82%[b]
8	 25	 34	70%[b]
9	 26	 35	66%[b]

[a] All yields refer to isolated, pure products. [b] Trifluoroacetylation was conducted at −78 °C.

trifluoroacetate release, and again, good to high yields of the enones **27**−**35** were obtained. Additional evidence of the utility of this process was found in the case of α-thujone **22**, because no epimerization of the α-stereocenter was observed by ^{1}H NMR. Furthermore, similar to the targeted substrate **3** (see Scheme 1), the formation of the olefin product **31** from α-thujone **22** was significant due to the steric bulk at the positions neighboring the α-carbon of **22**. Good yields from the two-step α-methylenation by trifluoroacetate release were obtained with carbonyl groups in acyclic systems, five-, six-, and seven-membered rings, and across ketones, lactams, and lactones. Also, (*R*)-carvone **21** was converted to the triene **30** in 85% yield without any evidence of olefin migration.

With these successes, we turned our attention to more complex natural products and further decided to compare the isolated yields from deformylative olefination to detrifluoroacetylative olefination. From the side-by-side comparisons, our olefination via trifluoroacetate release provided significantly higher yields than the respective deformylative olefination (Table 3). For

Table 3. Scope of Two-step Conversion of Carbonyl Groups to Enones by Trifluoroacetate Release

			olefination yield[a]	
entry	substrate	product	via formylation[c]	via trifluoro-acetylation[b]
1	**3**	**5**	28%	65%
2	 **36**	 **40**	0%	85%
3	 **37**	 **41**	36%	64%
4	 **38**	 **42**	trace	59%
5	 **39**	 **43**	0%	28%

[a] All yields refer to isolated, pure products. [b] LiHMDS, $CF_3CO_2CH_2CF_3$, THF, then K_2CO_3, $(CH_2O)_n$, 18-crown-6, benzene, reflux. [c] See ref 15b.

example, using the two-step protocol for olefination by trifluoroacetate release, the isolated yield of the desired sclareolide derivative **5** was increased to 65%, which is more than double the yield compared to formyl group release. An extreme case is the diolefination of the tropinone derivative **36** whereby trifluoroacetate release provided the diolefin in high 85% yield, but the olefination by formate release failed to form any product. A similar result occurred in the conversion of the natural product, (−)-eburnamonine (**39**), to its olefin derivative **43**. Even though the isolated yield from trifluoroacetate release provided the product in a low 28% yield, this alkaloid has a tertiary amine (i.e., a nucleophile) that confounds the generation of the electrophilic enone group. In the case of steroid **37**, no epimerization of the α-stereocenter was observed in enone **41** by ^{1}H NMR. The formation of the enone products from the natural products (+)-sclareolide **3** and (−)-eburnamonine **39** demonstrate the intended utility of this approach by trifluoroacetate release, because there is significant steric bulk at the positions neighboring the α-position (see also Scheme 1).

To obtain mechanistic information about the release of trifluoroacetate, we monitored the progress of the conversion of **6** to **12** by ^{1}H and ^{19}F NMR. The starting material **6** has a trifluoromethyl group that provides a chemical shift of −73.5 ppm by ^{19}F NMR (Figure 2). We subjected this substrate to the olefination conditions promoted by trifluoroacetate release and obtained ^{19}F NMR spectra at 30 min intervals. The substrate **6** was completely consumed after 30 min. Because the reaction solvent is benzene, the trifluoroacetate that is generated during the formation of the olefin is not soluble. However, it can be observed upon the addition of water prior to observation by ^{19}F NMR (data not shown). Using the mechanistic interpretation of Murray and Reid for deformylative olefination,[15b] we propose a

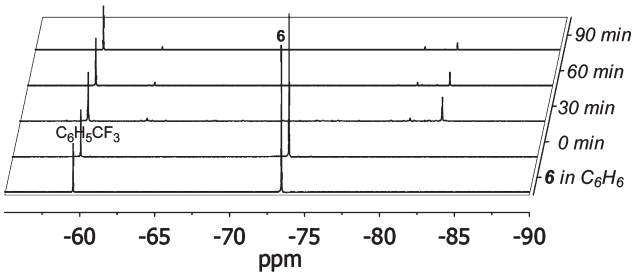


Figure 2. ^{19}F NMR spectroscopy of **6** in benzene with $(CH_2O)_n$ and K_2CO_3 across 90 min at 30 min intervals. The internal standard is $C_6H_5CF_3$.

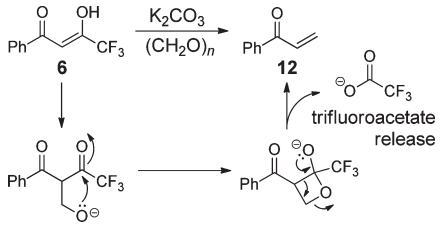
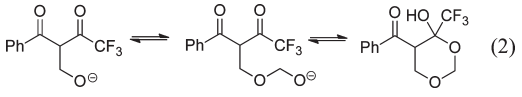


Figure 3. Plausible mechanism for olefination by trifluoroacetate release.

mechanism in which trifluoroacetate is rapidly released after the formation of a four-membered ring intermediate (Figure 3). The ^{19}F NMR at −83.0 ppm was quite interesting, and we obtained additional structural detail to determine if this transient peak could be attributed to a mechanistic intermediate depicted in Figure 3 or another intermediate. Indeed, the compound responsible for this rogue peak could not be isolated after aqueous workup and purification. To determine its identity, we obtained ^{1}H, ^{13}C, HMBC, and HMQC NMR data, and after our analysis, a 4-(trifluoromethyl)-1, 3-dioxan-4-ol structure was assigned (eq 2).[27] Indeed, methods to prepare compounds with a 4-(trifluoromethyl)-1,3-dioxan-4-ol structure are rare.[28] This intermediate could be envisioned to form after the addition of a second equivalent of formaldehyde and cyclization on the trifluoromethyl ketone as in eq 2. Multiple additions of formaldehyde to a substrate are known in the literature during the formation of 1,3-dioxanes[29] and of 1,3,5-dioxathiocane.[30] Because the compound is only transiently formed, we assert that its formation is reversible and has little effect on the overall process, which is quite rapid.



With the series of natural products and natural product derivatives in hand, we performed a preliminary screen for biological activity in an antiproliferative assay with HL-60 (human acute promyelocytic leukemia) cells to compare the compounds **1**, **3**, **5**, **21**, **22**, **30**, **31**, and **36**−**43** (Figure 4). Each compound was tested at 5 and 50 μM concentration, as screening strategies using one concentration[31] or two concentrations[32] can rapidly identify biologically active molecules. Parthenolide (**1**) served as a positive control and its activity in our assay is similar to previous reports.[33] This natural product has a mechanism of action through covalent binding.[34] (+)-Sclareolide (**3**) is weakly active at both test concentrations, but the derivative **5** with an α-methylene group has increased activity at 50 μM. Likewise, the carvone derivative **30** is active in the assay at high concentration, and tropinone analogue **40** is highly active at both concentrations, but the parent compounds (i.e., **21** and **36**, respectively) are inactive.

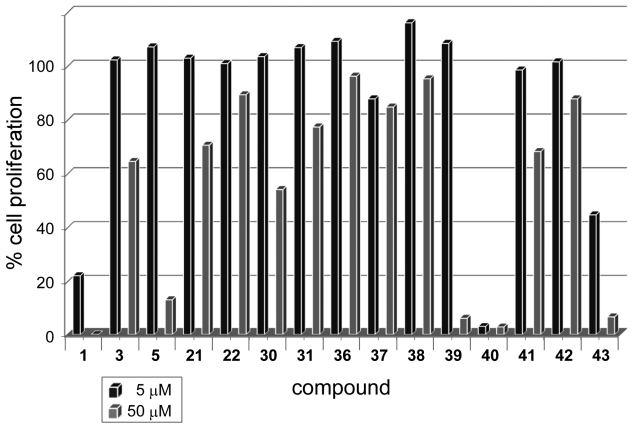


Figure 4. Antiproliferative assay with HL-60 cells. The HL-60 cells were incubated with compound for 72 h at 5 and 50 μM concentrations. Each test was performed in quadruplicate and the antiproliferative effects are displayed as the average of the four values.

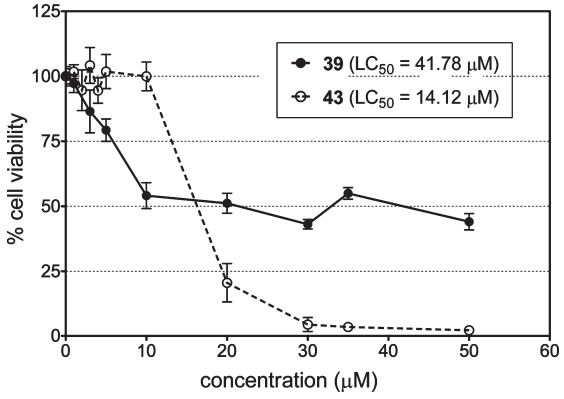


Figure 5. Cytotoxicity assay with MDA-MB-231 cells. The MDA-MB-231 cells were incubated with **39** or **43** for 96 h. All values were normalized to cell viability of vehicle treated controls and each represents the average of three independent experiments performed in triplicate.

On the other hand, the additional presence of an enone did not always impart biological activity upon a molecule. In the cases of the derivatives of thujone, pregnenolone, and androsterone, neither the parent compounds **22**, **37**, or **38** nor the enone containing derivatives **31**, **41**, or **42** showed inhibition of HL-60 proliferation in the assay. (−)-Eburnamonine (**39**) has biological activity as a muscarinic agonist,[35] but previous tests showed no cytotoxicity against KB (human oral epidemoid carcinoma) cells.[36] In our antiproliferative assay, it displays significant antiproliferative effects activity in HL-60 cells at 50 μM. The eburnamonine analogue **43** appears to be more potent than **39** in HL-60 cells, because antiproliferative effects are observed at both 5 and 50 μM. In order to further compare the biological activity of **39** and **43**, we conducted a more thorough biological evaluation in MDA-MB-231 cells, which are metastatic breast cancer cells with the multidrug-resistance phenotype. This cell line is highly aggressive and is known to be resistant to multiple chemotherapeutic agents.[37] Thus, MDA-MB-231 cells were treated with increasing concentrations of **39** and **43** (Figure 5). Both compounds exhibited cytotoxicity with LC_{50} values of 41.78 μM (95% confidence interval of 30−58 μM) and 14.12 μM (95% confidence interval of 10−17 μM) for **39** and **43**, respectively. Based on ANOVA results, **43** was significantly more cytotoxic than

39 (p = 0.0008), and at doses ≥30 μM, **43** was able to eliminate nearly 100% of cells, while the cytotoxic effect of (−)-eburnamonine **39** plateaued between 10 and 30 μM with resistance observed to the doses as high as 1 mM (data not shown in Figure 5). Overall, these biological data support that the added presence of an enone may enhance biological activity, but this relationship is not universal and the relative magnitude of the effects may depend on additional factors. Furthermore, the selective incorporation of an enone may also impart an additional mechanism of action through covalent binding. Additional studies are underway to determine the increased antiproliferative effects of the (−)-eburnamonine derivative **43**.

■ CONCLUSIONS

In conclusion, we have developed a novel method to install methylene groups at the α-position of carbonyl groups using the facile release of trifluoroacetate, which is rarely used in organic synthesis. Our method represents an improvement beyond existing protocol in cases of steric hindrance and sensitive functional groups, and we have demonstrated the utility of the process across a series of ketones, lactams, and lactones. We were also successful in preparing semisynthetic derivatives of complex natural products. Additionally, we have provided mechanistic insight for the process using ^{19}F NMR data that indicate that the olefination proceeds very rapidly. Biological evaluation led to the identification of a derivative of (−)-eburnamonine with significant cytotoxicity in drug-resistant MDA-MB-231 breast cancer cells. Future studies will describe new avenues for the use of trifluoroacetate release in synthesis and provide additional structure−activity relationships for this novel semisynthetic derivative of (−)-eburnamonine.

■ EXPERIMENTAL SECTION

General Procedure A for Detrifluoroacetylative Olefination. To a solution of 4,4,4-trifluoro-1-phenyl-1,3-butanedione **6** (42 mg, 0.19 mmol) in benzene (10 mL) were added K_2CO_3 (82 mg, 0.59 mmol) and paraformaldehyde (200 mg, 6.59 mmol), and the mixture was heated to reflux (oil bath = 90 °C). After 2 h the reaction mixture was allowed to cool to rt, saturated aqueous NH_4Cl (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (15% EtOAc in hexanes) afforded the phenyl vinyl ketone **12** as a yellow oil (24 mg) in 93% yield.[38]

General Procedure B for Detrifluoroacetylative Olefination. To a solution of 3-(trifluoroacetyl)camphor **11** (45 mg, 0.19 mmol) in benzene (10 mL) were added K_2CO_3 (82 mg, 0.59 mmol), 18-crown-6 (13 mg, 0.05 mmol), and paraformaldehyde (200 mg, 6.59 mmol). The suspension was heated to 80 °C for 2 h and then heated to reflux (oil bath = 90 °C) for 4 h. The mixture was allowed to cool to rt, saturated aqueous NH_4Cl (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (5% Et_2O in hexanes) afforded the α-methylene camphor **17** as a pale yellow oil (32 mg) in 95% yield.[38]

General Procedure C for Trifluoroacetylation/Detrifluoroaceylative Olefination. To a 0 °C solution of LiHMDS (0.65 mL, 0.6 M in THF) was added a solution of 1-indanone **20** (26 mg, 0.19 mmol) in THF (1.0 mL). The reaction mixture was allowed to warm to rt over 20 min, and then $CF_3CO_2CH_2CF_3$ was added (55 μL, 0.41 mmol). After an additional 20 min at rt, saturated aqueous NH_4Cl (5 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 5 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. Without purification, the crude mixture was immediately subjected to general procedure B. SiO_2 flash chromatography (25% EtOAc in hexanes) afforded the 2-methlyene-1-indanone **29** as a yellow oil (28 mg) in 98% yield.[38]

Phenyl Vinyl Ketone (12). See representative reaction procedure A. ^{1}H NMR, ^{13}C NMR, and LRMS data were identical with the reported data.[38,39]

***p*-Chlorophenyl Vinyl Ketone (13).** See representative reaction procedure A. SiO_2 flash chromatography (5% Et_2O in hexanes) afforded the title compound as a clear oil (27 mg) in 83% yield. ^{1}H NMR and IR data were identical with the reported data.[38,40]

Naphthyl Vinyl Ketone (14). See representative reaction procedure A. SiO_2 flash chromatography (20% Et_2O in hexanes) afforded the title compound as a yellow oil (27 mg) in 76% yield. ^{1}H and ^{13}C NMR data were identical with the reported data.[38,41]

Thienyl Vinyl Ketone (15). See representative reaction procedure A. SiO_2 flash chromatography (10% Et_2O in hexanes) afforded the title compound as a colorless oil (26 mg) in 98% yield. ^{1}H NMR, IR, and LRMS data were identical with the reported data.[38,42]

1,3-Benzodioxoly Vinyl Ketone (16). See representative reaction procedure B. SiO_2 flash chromatography (15% EtOAc in hexanes) afforded the title compound as a colorless oil (20.9 mg) in 61% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 1.5 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.12 (dd, J = 17.0, 10.5 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.42 (dd, J = 17.0, 1.5 Hz, 1H), 6.06 (s, 2H), 5.87 (dd, J = 10.5, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 151.9, 148.3, 132.0 (2), 129.5, 125.1, 108.5, 107.9, 101.9; IR (film) ν_{max} 2900, 1661, 1443, 1250 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_8O_3$ $(M)^+$ 176.0473, found 176.0470.

α-Methylene-camphor (17). See representative reaction procedure B. ^{1}H NMR and IR data were identical with the reported data.[38,43]

2-Methyl-1-phenylprop-2-ene-1-one (27). See representative reaction procedure C. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compounds as a colorless oil (26 mg) in 92% yield. ^{1}H NMR, IR, and HRMS data were identical with the reported data.[38,44]

Adamantyl Vinyl Ketone (28). See representative reaction procedure C. SiO_2 flash chromatography (1% EtOAc in hexanes) afforded the title compound as a colorless oil (30 mg) in 88% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, J = 17.1, 10.5 Hz, 1H), 6.32 (dd, J = 17.1, 2.4 Hz, 1H), 5.63 (dd, J = 10.5, 8.4 Hz, 1H), 2.06 (m, 3H), 1.81 (d, J = 2.7 Hz, 6H), 1.79−1.64 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 130.7, 128.6, 45.6, 38.0 (3), 36.9 (3), 28.2 (3); IR (film) ν_{max} 2905, 2851, 1687, 1017 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{18}O$ $(M)^+$ 190.1358, found 190.1356.

2-Methylene-1-indanone (29). See representative reaction procedure C. ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were identical with the reported data.[38,45]

α-Methylene-(*R*)-carvone (30). See representative reaction procedure C. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound as a pale yellow oil (26 mg) in 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (tt, J = 5.0, 1.0 Hz, 1H), 6.06 (t, J = 1.8 Hz, 1H), 5.19 (t, J = 1.8 Hz, 1H), 4.92 (t, J = 1.5 Hz, 1H), 4.77 (m, 1H), 3.39 (t, J = 6.5 Hz, 1H), 2.57−2.43 (m, 2H), 1.82 (q, J = 1.8 Hz, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 145.1, 144.3, 144.0, 136.0, 120.6, 113.6, 48.6, 30.0, 20.5, 16.1; IR (film) ν_{max} 2923, 1667, 1614, 1048 cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_{14}O$ $(M)^+$ 162.1045, found 162.1048; $[\alpha]^{25}_D$ −31.2 (c 1.82, CH_2Cl_2).

α-Methylene-thujone (31). See representative reaction procedure C. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound as a colorless oil (27 mg) in 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (s, 1H), 5.31 (s, 1H), 2.35 (q, J = 7.5 Hz, 1H), 1.97 (qu, J = 7.0 Hz, 1H), 1.30 (dd, J = 8.0, 4.5 Hz, 1H), 1.14 (d, J = 7.5 Hz, 3H), 1.13 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.36 (t, J = 5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 148.5, 115.9, 45.7, 35.4, 29.7, 25.2, 20.6, 20.5, 19.1, 18.3; IR (film) ν_{max} 2961, 2918,

1749 cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_{16}O$ $(M)^+$ 164.1201, found 164.1199; $[\alpha]^{25}_D$ −26.1 (c 0.65, $CHCl_3$).

***N-tert*-Butylcarbamate-2-methylene-ε-caprolactam (32).** See representative reaction procedure C. SiO_2 flash chromatography (50% EtOAc in hexanes) afforded the title compound as a colorless oil (36.7 mg) in 83% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (s, 1H), 5.38 (s, 1H), 3.66 (t, J = 5.0 Hz, 2H), 2.42 (t, J = 5.0 Hz, 2H), 1.79−1.68 (m, 4H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 152.7, 147.2, 123.2, 82.6, 46.0, 32.5, 29.1, 28.1 (3), 28.0; IR (film) ν_{max} 2934, 1761, 1707, 1180, 1141 cm^{-1}; HRMS (CI) m/z calcd for $C_{12}H_{19}NO_3$ $(M + H - C_4H_8)^+$ 170.0817, found 170.0814.

(3*S-cis*)-(+)-Tetrahydro-3-isopropyl-7a-methyl-6-methylenepyrrolo[2,1-*b*]oxazol-5(6*H*)-one (33). See representative reaction procedure C. The trifluoroacetylation step was conducted at −78 °C. SiO_2 flash chromatography (15% EtOAc in hexanes) afforded the title compound as a colorless oil (31.5 mg) in 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 5.5, 3.5 Hz, 1H), 7.52 (dd, J = 5.5, 3.5 Hz, 1H), 4.21 (m, 2H), 1.68 (septet, J = 6.0 Hz, 1H), 1.48−1.37 (m, 2H), 1.33−1.25 (m, 4H), 0.92 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 132.3, 130.8, 128.7, 68.0, 38.6, 30.2, 23.6, 22.9, 14.0, 10.9; IR (film) ν_{max} 2918, 1729, 1272 cm−1; HRMS (EI) m/z calcd for $C_{11}H_{17}NO_2$ $(M)^+$ 195.1259, found 195.1262; $[\alpha]^{20}_D$ −0.007 (c 0.78, $CHCl_3$).

5-Hexyl-3-methylenedihydrofuran-2(3*H*)-one (34). See representative reaction procedure C. The trifluoroacetylation step was conducted at −78 °C. ^{1}H and ^{13}C NMR were identical with the reported data.[38,46]

(1*S*,5*R*)-α-Methylene-2-oxabicyclo[3.3.0]oct-6-en-3-one (35). See representative reaction procedure C. The trifluoroacetylation step was conducted at −78 °C. SiO_2 flash chromatography (25% EtOAc in hexanes) afforded the title compound as a colorless oil (20 mg) in 66% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (d, J = 2.0 Hz, 1H), 5.76 (td, J = 4.9, 2.4 Hz, 1H), 5.68 (d, J = 1.7 Hz, 1H), 5.54 (dt, J = 4.9, 2.1 Hz, 1H), 5.10 (t, J = 6.2 Hz, 1H), 4.03 (ddt, J = 5.9, 3.8, 1.9 Hz, 1H), 2.85−2.76 (m, 1H), 2.74−2.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 136.4, 130.2, 129.6, 121.9, 80.1, 50.8, 39.4; IR (film) ν_{max} 2923, 1762, 1665, 1400, 1016 cm^{-1}; HRMS (EI) m/z calcd for $C_8H_8O_2$ $(M)^+$ 136.0524, found 136.0526; $[\alpha]^{20}_D$ = −25.3 (c 0.14, $CHCl_3$)

11-Methylene-(+)-sclareolide (5). See representative reaction procedure C. SiO_2 flash chromatography (15% EtOAc in hexanes) afforded the title compound as a yellow oil (32 mg) in 65% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (d, J = 3.5 Hz, 1H), 5.47 (d, J = 3.5 Hz, 1H), 2.51 (t, J = 3.0 Hz, 1H), 2.10 (dt, J = 12.0, 3.5 Hz, 1H), 1.96 (dtd, J = 13.0, 3.5, 1.5 Hz, 1H), 1.89 (ddd, J = 14.5, 4.0, 3.0 Hz, 1H), 1.78−1.66 (m, 2H), 1.52−1.33 (m, 3H), 1.29 (s, 3H), 1.25−1.15 (m, 2H), 1.08 (dd, J = 13.0, 3.0 Hz, 1H), 1.05 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 137.6, 118.4, 84.8, 64.2, 57.2, 42.3, 39.1, 38.2, 37.6, 33.7, 33.6, 23.8, 21.3, 20.7, 18.4, 15.6; IR (film) ν_{max} 2949, 1765, 1020, 930 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{26}O_2$ $(M + H)^+$ 263.2011, found 263.2002; $[\alpha]^{25}_D$ +15.0 (c 1.45, $CHCl_3$).

2,7-Dimethylene-tropinone (40). See representative reaction procedure C. *N*-ethyl carbamate tropinone (**36**) was prepared according to the literature procedure.[47] LiHMDS (4 equiv) and $CF_3CO_2CH_2CF_3$ (4 equiv) were used for trifluoroacetylation. For the olefination protocol, after heating to reflux for 4 h, the reaction mixture was cooled to 80 °C, and an additional portion of paraformaldehyde (200 mg) was added. After heating at this temperature for 4 h, the reaction mixture was heated to reflux (oil bath = 90 °C) for 2 h. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound as a yellow oil (37 mg) in 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (s, 2H), 5.37 (s, 2H), 4.95 (s, 2H), 4.11 (q, J = 7.0 Hz, 2H), 2.32 (m, 2H), 1.76 (dd, J = 8.0, 6.5 Hz, 2H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.4, 171.5, 154.3, 146.1, 146.0, 128.7, 61.8, 60.7, 59.0, 23.0, 21.4, 14.5; IR (film) ν_{max} 2981, 1705, 1692, 1105 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{15}O_3$ $(M + Na)^+$ 244.0950, found 244.0948.

α-Methylene-*tert*-butyl-dimethylsilyl-pregnenolone (41). See representative reaction procedure C. The *tert*-butyl-dimethylsilyl pregnenolone **37** was prepared according to the literature procedure.[48] SiO_2 flash chromatography (4% EtOAc in hexanes) afforded the title compound as a colorless solid (55 mg) in 64% yield: mp 119−121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (dd, J = 17.5, 10.5 Hz, 1H), 6.20 (dd, J = 17.5, 1.5 Hz, 1H), 5.67 (dd, J = 10.5, 1.5 Hz, 1H), 5.32 (m, 1H), 3.51−3.45 (m, 1H), 2.79 (t, J = 9.0 Hz, 1H), 2.32−2.14 (m, 4H), 2.03−1.93 (m, 2H), 1.80 (dt, J = 13.0, 3.5 Hz, 1H), 1.75−1.60 (m, 4H), 1.53−1.39 (m, 6H), 1.30−1.17 (m, 2H), 0.99 (s, 3H), 0.89 (s, 9H), 0.60 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 141.9, 137.5, 127.4, 121.2, 72.9, 61.2, 57.6, 50.4, 45.1, 43.1, 39.4, 37.7, 37.0, 32.4, 32.3, 32.2, 26.3 (3), 25.0, 23.1, 21.4, 19.8, 18.6, 13.8, −4.2 (2); IR (film) ν_{max} 2931, 1667, 1087 cm^{-1}; HRMS (EI) m/z calcd for $C_{28}H_{46}O_2Si$ $(M + H)^+$ 443.3345, found 443.3340; $[\alpha]^{25}_D$ +43.6 (c 0.1, $CHCl_3$).

α-Methylene-*tert*-butyl-dimethylsilyl-andosterone (42). See representative reaction procedure C. The *tert*-butyl-dimethylsilyl androsterone **38** was prepared according to the literature procedure.[49] SiO_2 flash chromatography (2% EtOAc in hexanes) afforded the title compound as a colorless solid (47 mg) in 59% yield: mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (m, 1H), 5.35 (m, 1H), 3.54 (tt, J = 10.8, 5.0 Hz, 1H), 2.55 (dd, J = 15.5, 6.5 Hz, 1H), 2.19−2.12 (m, 1H), 1.87−1.83 (m, 1H), 1.77−1.54 (m, 6H), 1.48−1.24 (m, 9H), 1.12−0.91 (m, 4H), 0.88 (s, 9H), 0.83 (s, 3H), 0.75−0.67 (m, 1H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 144.9, 118.8, 72.3, 54.9, 49.0, 48.3, 45.3, 38.9, 37.4, 36.1, 34.9, 32.2, 31.9, 31.4, 29.6, 28.8, 26.3 (3), 20.8, 18.6, 14.5, 12.7, −4.2 (2); IR (film) ν_{max} 2927, 2854, 1728, 1641, 1091 cm^{-1}; HRMS (EI) m/z calcd for $C_{26}H_{44}O_2Si$ $(M + H)^+$ 417.3189, found 417.3186; $[\alpha]^{25}_D$ +11.9 (c 2.1, $CHCl_3$).

α-Methylene-(−)-eburnamonine (43). See representative reaction procedure C. SiO_2 PTLC (79% EtOAc; 29% hexanes; 1% Et_3N) afforded the title compound as a yellow oil (17 mg) in 28% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.36−7.28 (m, 2H), 6.66 (s, 1H), 5.73 (s, 1H), 4.14−4.12 (m, 1H), 3.36 (dd, J = 14.0, 6.5 Hz, 1H), 3.28−3.22 (m, 1H), 2.98−2.91 (m, 1H), 2.64−2.60 (m, 1H), 2.57−2.47 (m, 2H), 2.36 (sextet, J = 7.5 Hz, 1H), 1.93−1.83 (m, 2H), 1.45−1.40 (m, 1H), 1.38−1.25 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 145.2, 134.8, 131.5, 130.7, 125.8, 124.7, 124.4, 118.4, 116.9, 113.1, 54.4, 51.3, 44.5, 43.2, 32.2, 24.6, 21.3, 16.9, 8.8; IR (film) ν_{max} 2936, 1692, 1455, 1092 cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{22}N_2O$ $(M)^+$ 306.1732, found 306.1736; $[\alpha]^{25}_D$ −31.4 (c 0.34, CH_2Cl_2); UV (CH_3CN) λ_{max} (log ε) 255 (1.71), 265 (1.65) nm.

Cell Culture for HL-60 Cells[33]. HL-60 (human promyelocytic leukemia) cells were obtained from ATCC. The cell culture was transition into and then maintained in phenol red free RPMI-1640, supplemented with 10% fetal bovine serum, and filter sterilized. Cells were cultured at 37 °C in a humidified incubator under 5% CO_2 in air and passaged as recommended.

Cell Proliferation Assay in HL-60 Cells[33]. The values for HL-60 cell proliferation in the presence of enone **1**, **3**, **5**, **21**, **22**, **30**, **31**, and **36**−**43** were determined by MTT assay. HL-60 cells were plated into a 96-well plate at 5,000 cells per well in 80 μL. The cells were treated with 20 μL of a solution of test compound for a final concentration of 5 and 50 μM in 0.5% DMSO in growth medium. Each concentration was repeated in quadruplicate, and the plate was incubated at 37 °C in a humidified incubator under 5% CO_2 in air. After incubation for 72 h, 20 μL of MTT solution (2.5 mg/mL) in serum-free RPMI-1640 was added to each well, and the plate was incubated further for 4 h. Next, 100 μL of acidic isopropyl alcohol (10% Triton X-100 plus 0.1 N HCl in anhydrous isopropyl alcohol) was added and allowed to dissolve for 16 h. The OD was measured at 570 nm, and the values for HL-60 cell proliferation were calculated by GraphPad Prism 5 software.

Cell Culture for MDA-MB-231 Cells. MDA-MB-231 cells were obtained from ATCC and cultured in complete media [DMEM supplemented with 4500 mg/L glucose, L-glutamine, $NaHCO_3$, pyridoxine·HCl,

and 10% fetal bovine serum]. Cells were cultured at 37 °C in a humidified incubator under 5% CO_2 in air and passaged as recommended.

Cytotoxicity Assay in MDA-MB-231 Cells. The LC_{50} values for MDA-MB-231 cells in the presence of enone **39** and **43** were determined by MTS assay. MDA-MB-231 cells were seeded in 96-well plate at 20,000 cells/well and treated for 96 h with either DMSO vehicle control or various doses of **39** and **43**. MTS assay was performed using the CellTiter 96 AQ_{ueous} Non-Radioactive Cell Proliferation Assay (MTS) assay kit (Promega) per manufacturer instructions. Briefly, 20 μL of the combined MTS/PMS solution was added to each well and incubated for 90 min at 37 °C under 5% CO_2 in air. The OD was subsequently read at 492 nm on a Thermo Multiscan Asent plate reader. Data are presented as mean ± SEM of at least 3 independent experiments performed in triplicate. LC_{50} values were calculated by four-parameter logistic regression applied to log-transformed percent viability measurements. Significance was analyzed by a two-way analysis of variance (ANOVA) and Bonferroni's correction as post-test to compare experiments with multiple parameters. *P*-values below 0.05 were considered statistically significant. All analyses were performed using Prism 5.0 software (GraphPad Software).

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra, X-ray data, and preparation of compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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