

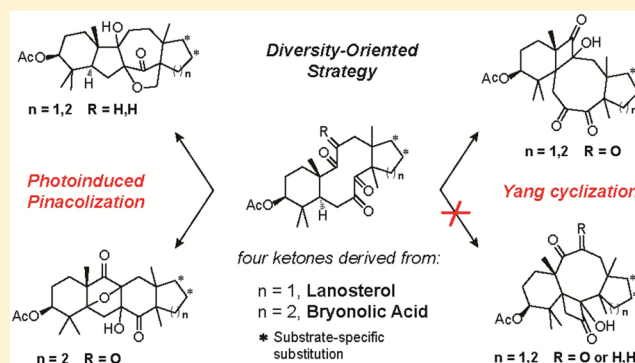
Approach for Expanding Triterpenoid Complexity via Divergent Norrish-Yang Photocyclization

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S Supporting Information

ABSTRACT: Triterpenoids comprise a very diverse family of polycyclic molecules that is well-known to possess a myriad of medicinal properties. Therefore, triterpenoids constitute an attractive target for medicinal chemistry and diversity-oriented synthesis. Photochemical transformations provide a promising tool for the rapid, green, and inexpensive generation of skeletal diversity in the construction of natural product-like libraries. With this in mind, we have developed a diversity-oriented strategy, whereby the parent triterpenoids bryonolic acid and lanosterol are converted to the pseudosymmetrical polyketones by sequential allylic oxidation and oxidative cleavage of the bridging double bond at the B/C ring fusion. The resultant polyketones were hypothesized to undergo divergent Norrish-Yang cyclization to produce unique 6/4/8-fused triterpenoid analogues. The subtle differences between parent triterpenoids led to dramatically different spatial arrangements of reactive functionalities. This finding was rationalized through conformational analysis to explain unanticipated photoinduced pinacolization, as well as the regio- and stereochemical outcome of the desired Norrish-Yang cyclization.



INTRODUCTION

Triterpenoids are a broad and structurally diverse class of natural products primarily derived from the plant kingdom.¹ The triterpenoid family consists of nearly 30 000 members with over 200 unique carbocyclic skeletons.^{2,3} Consequently, triterpenoids are known to have a wide array of biological activities, including antifungal,⁴ anti-inflammatory,⁵ anticancer,^{6,7} as well as antiviral⁸ and antibacterial properties.⁹ This remarkable molecular and medicinal diversity among triterpenoids is achieved through the variety of squalene and oxidosqualene cyclases that catalyze these reactions,¹⁰ as well as through further modification of the carbon skeletons by minor rearrangements including homologation, cleavage, and degradation (Figure 1).

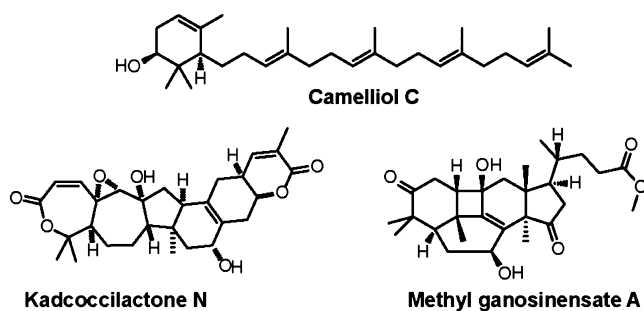


Figure 1. Selected members of the triterpenoid family.

Considerable efforts in drug discovery have focused on the isolation and structural elucidation of novel triterpenoid molecules from the plant sources.^{11–13} Moreover, semi-synthetic triterpenoids, created by further manipulation of the exterior functional groups, have been shown to enhance the potency of their natural precursors.^{14–16} In this regard, the increase in structural complexity of triterpenoid-like molecules through alteration of their carbocyclic core skeleton can be viewed as a promising tool to study the chemical biology and medicinal chemistry of this natural product family.^{17,18}

The use of photochemical transformations for the target-oriented synthesis of complex natural products has proven to be an effective approach.^{19,20} The advantages of these reactions are the green and low-cost nature of the reagent, as well as the fact that such transformations allow for the rapid construction of strained systems that otherwise would be very difficult to synthesize. However, the use of light as a reagent in diversity-oriented synthesis is limited.^{21,22} In relation to natural products, a single report by the group of de la Torre²³ describes an elegant application of a [2 + 2] cycloaddition and Paterno-Buchi reaction to the synthesis of diverse polycyclic terpene-like structures from readily available sesquiterpene Sclareolide.

We set out to apply Norrish-Yang photocyclization^{24,25} (Figure 2a) to the synthesis of triterpenoid analogues with unique 6/4/8-fused ring systems. The Norrish-Yang reaction

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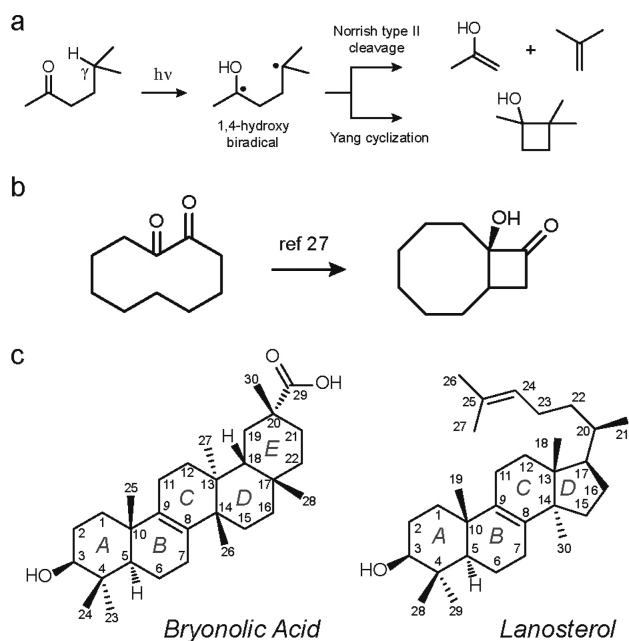


Figure 2. (a) General mechanism of Norrish-Yang type II photocyclization. (b) Formation of 4/8-fused carbocycle from 1,2-cyclodecanone. (c) Structures and carbon numbering of bryonolic acid and lanosterol.

was chosen because it allows for (1) selective C–C bond formation from unactivated sp^3 -hybridized C–H bonds of saturated hydrocarbons; and (2) formation of particular 4/8-fused carbocycles from cyclodecanone substrates^{26,27} (Figure 2b). Additionally, the 1,2-diketone moiety is known to be an excitable chromophore that can undergo Yang cyclization as opposed to the Norrish type II fragmentation.^{28–33}

The application of Yang cyclization to the construction of additional four-membered rings in steroids has been reviewed by Kamernitskii et al.³⁴ The diversity-oriented strategy^{35,36} which we have envisioned is different from earlier approaches in that the reactive keto groups are strategically positioned within a parent triterpenoid core structure by sequential oxidation reactions. This is followed by the generation of a new ring fusion via regioselective photocyclization.

Here, we report the successful application of this strategy to a pentacyclic triterpenoid, bryonolic acid, and a tetracyclic triterpenoid, lanosterol (Figure 2c). These molecules were chosen due to the unsaturation at the B/C ring fusion, which allowed for the formation of the desired cyclodecane-1,2-diones by the allylic oxidation and subsequent oxidative cleavage reactions. The resultant ketones were systematically studied for structural elements dictating the regio- and stereoselectivity of the following Norrish-Yang reaction.

RESULTS AND DISCUSSION

Tetraketone **1** was prepared according to our previously published method¹⁸ from doubly protected bryonolic acid in two steps by oxidation of the $\Delta^{8,9}$ double bond with ruthenium tetroxide under Sharpless conditions. Early analysis of the bichromophoric structure of tetraketone **1** revealed that the “bowsprit” hydrogen H-5 is in γ -position to the keto groups at C-8 and C-11. Thus, photoexcitation of the C-8 carbonyl bond could lead to the formation of cyclobutanol **2** via pathway b, and concurrently, photoexcitation of C-11 carbonyl would result in the formation of cyclobutanol **3** via pathway a (Table

1). When this rationale was taken into account, a solution of tetraketone **1** in dry deoxygenated C_6D_6 was irradiated in a

Table 1. Norrish-Yang Reactivity of Tetraketone **1**

entry	λ_{max} (nm)	time (min)	isolated yield of product (%)	
			3	4
1	254	45	33	10
2	300	90	63	13
3	350	135	30	5
4	300 ^a	45	56	<1

^aReaction was carried out in the presence of 1.0 equiv of benzophenone.

quartz cuvette with 254 nm UV light until complete consumption of the starting material was detected by TLC (45 min, Table 1, entry 1). Further investigation of the reaction mixture showed the formation of two products, which were separable by column chromatography on silica.

The study of the NMR spectra of the major reaction product revealed an AX system of two doublets at 3.40 and 2.75 ppm ($J = 12$ Hz) attached to isolated methylene carbon at 41.2 ppm. These protons correlate, as observed by HMBC, with two carbonyl carbons (C-7, δ_C 210.0; C-8, δ_C 211.5), as well as with four quaternary carbons (C-4, δ_C 43.8; C-5, δ_C 56.9; C-10, δ_C 62.3; C-11, δ_C 92.2). These correlations allowed the assignment of the AX system to position 6 of the cyclobutanol **3** and ruled out structure **2**, in which H-6 could only be correlated to one carbonyl carbon by HMBC spectroscopy. Further investigation of the structure of cyclobutanol **3** disclosed an AX system of two doublets at 2.25 and 1.73 ppm ($J = 18$ Hz), attached to another isolated methylene carbon C-12 (δ_C 42.4). In the HMBC spectrum, H-12 showed cross-peaks with one carbonyl carbon (C-9, δ_C 218.9), as well as one methine carbon (C-18, δ_C 47.0), one methyl carbon (C-27, δ_C 19.0), and four quaternary carbons (C-5, C-11, C-13, δ_C 40.6; C-14, δ_C 55.4). Consequently, the NMR and the HRMS data were consistent with the proposed structural framework of cyclobutanol **3** (Figure 3).

The routine NMR spectra of the minor reaction product were inconsistent with a structure of a product of Yang cyclization of tetraketone **1**. Specifically, examination of ^{13}C NMR spectrum revealed the signals of two carbonyl carbons (C-8, δ_C 212.6; C-9, δ_C 212.4), as well as three quaternary carbons (C-5, δ_C 90.6; C-7, δ_C 90.3; C-11, δ_C 77.3) in the region downfield from 50 ppm. Extensive 2D NMR experiments allowed us to propose structure **4** for the minor product of the reaction. Especially useful were the cross-peaks shown by two doublets at 2.69 and 1.88 ppm (H-6, $J = 14$ Hz), attached

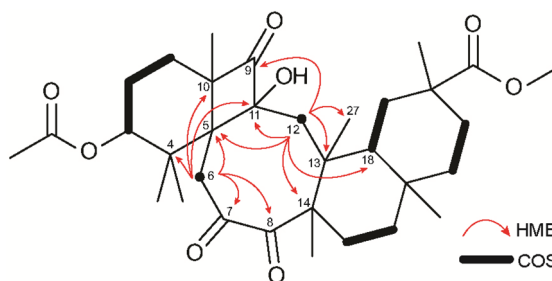


Figure 3. Key HMBC (^1H to ^{13}C) and COSY correlations of cyclobutanol 3.

to an isolated methylene carbon C-6 (δ_{C} 39.8). In the HMBC spectrum, H-6 correlated to C-5, C-7, C-8, as well as C-10 (δ_{C} 48.7) and C-11. Additionally, the correlations of two doublets at 2.20 and 1.97 ppm (H-12) in the HMBC spectrum supported the elucidation of the carbon framework of structure 4 by showing the cross-peaks with C-7, C-9, C-11, as well as C-13 (δ_{C} 40.4), C-14 (δ_{C} 52.5), C-18 (δ_{C} 44.3), and C-27 (δ_{C} 22.3) (Figure 4). The structural assignment was also supported by HRMS data.

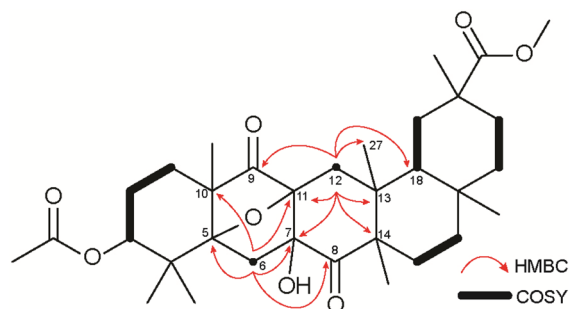


Figure 4. Key HMBC (^1H to ^{13}C) and COSY correlations of structure 4.

After elucidation of the structures of the reaction products, the yields of cyclobutanol 3 and the minor product of the photolysis 4 were found to be 33 and 10%, respectively (Table 1, entry 1). The changing of the light sources did not lead to substantial difference in product distribution; however, the highest combined yield of 3 and 4 was achieved with a 300 nm UV lamp (76%, Table 1, entry 2). It is noteworthy that no products of the type II photofragmentation were observed in any reactions performed.

To gain insight into the regio- and, more importantly, stereochemical outcome of the Yang cyclization of tetraketone 1, we next examined a plausible mechanism for the process. It has been determined by the Scheffer group^{37–39} that, in order for a ketone to undergo successful Norrish type II hydrogen abstraction reaction, the distance between the oxygen of the carbonyl and the γ -H has to be less than the sum of van der Waals radii for the H and O (2.72 Å). Using B3LYP/6-311G(d,p) calculated geometry of tetraketone 1, we determined that only the C-11 keto group met this requirement ($d_1 = 2.29$ Å, Figure 5), while the carbonyl at C-8 exceeded the suggested distance ($d_2 = 2.95$ Å). Consequently, irradiation of tetraketone 1 led exclusively to the formation of 1(C-5),4(C-11)-hydroxy biradical, which is geometrically predisposed to cyclize into *cis*-cyclobutanol 3. The intermediate hydroxy biradical can concurrently undergo photopinacolization^{40–43}

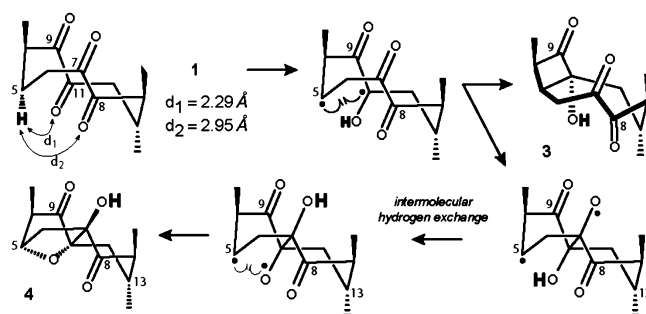


Figure 5. Mechanistic considerations for the formation of 3 and 4.

with the C-7 carbonyl leading to a C-5,O-7-centered biradical, which presumably can experience intermolecular H-exchange, followed by a ring closure to form bridged structure 4 (Figure 5).

The mechanistic rationale of the reaction is in complete agreement with the observed stereochemistry of the products 3 and 4, as determined by NOE correlation spectroscopy (Figure 6), demonstrating memory of chirality effect, whereby the chiral information of the tetraketone 1 is retained by the conformation of the biradical intermediate.^{44–47}

In the NOESY spectrum of cyclobutanol 3, H_{β} -6 correlates with H-25 and H-24 while H_{α} -6 correlates with H-23 and H-27, and the NOE interactions of H_{β} -12 with H-25 and H-26 determine α -facial orientation of the hydroxyl group at C-11. In the case of the bridged structure 4, H_{α} -6 correlates with H-24 and H-27 while H_{β} -6 correlates with H-25, as well as with the C7–OH hydroxyl group, which, in turn, shows an interaction with H-26. This provided evidence for the β -facial orientation of this hydroxyl group.

In an effort to force Yang cyclization into the alternative direction to form cyclobutanol 6, we took triketone 5 as a substrate for the photoreaction. The synthesis of triketone 5 by direct oxidation of doubly protected bryonolic acid with ruthenium tetroxide under Sharpless conditions was previously reported by our group.¹⁸ The structure of triketone 5 preserves the main structural features of tetraketone 1 but lacks the keto group at C-11 (Table 2).

The computed distance between H-5 and the oxygen of the C-8 carbonyl of triketone 5 is 2.56 Å, suggesting the high possibility of the desired transformation. In addition, the 1(C-7),2(C-8)-dione system becomes the major chromophore of the polyketone. Accordingly, irradiation of triketone 5 with 254 nm UV light for 72 h yielded a single reaction product (6% isolated yield, Table 2, entry 1). However, the structure of the product of the photolysis of triketone 5 was formulated as 7 on the basis of a thorough NMR investigation (Figure 7).

The ^{13}C NMR spectrum of 7 showed the presence of one carbonyl carbon C-8 (δ_{C} 212.9), as well as newly formed quaternary carbons C-7 (δ_{C} 87.3) and C-9 (δ_{C} 78.9), and a methylene carbon C-26 (δ_{C} 72.6) in the fingerprint region. This observation alone excludes structure 6, which would be expected to have two signals of the ketone groups in the ^{13}C spectrum. The ^1H NMR of 7 exhibited a pair of doublets at 4.29 and 4.04 ppm ($J = 10$ Hz), corresponding to a methylene carbon C-26 (δ_{C} 72.6). In the HMBC spectrum, H-26 showed cross-peaks with C-7, C-8, C-13 (δ_{C} 39.7), C-14 (δ_{C} 53.9), and a methylene carbon C-15 (δ_{C} 25.6). Structural assignment was completed by further analysis of cross-peaks shown by H-5, H-11, and H-25 (Figure 7), as well as HRMS data.

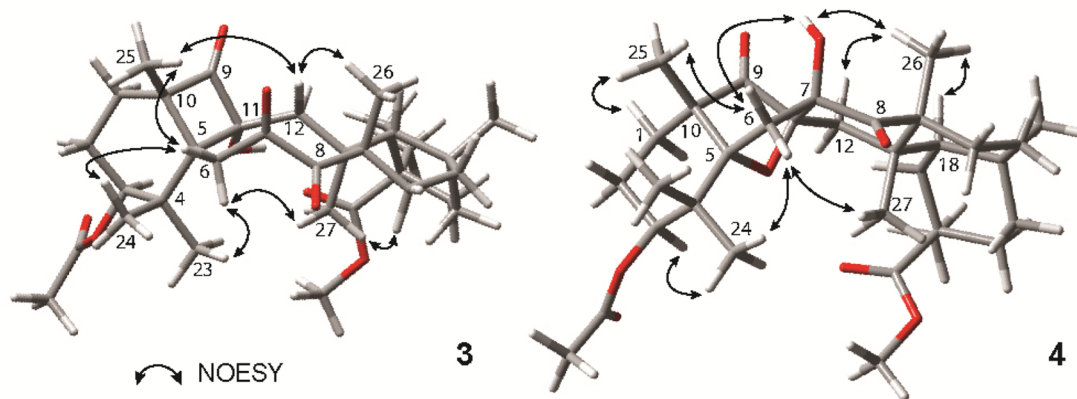
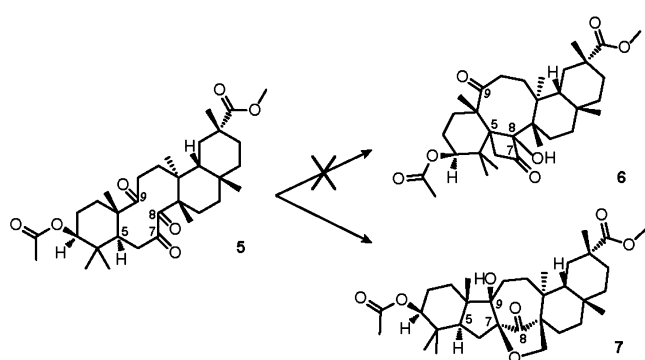


Figure 6. Key NOESY correlations of compounds 3 and 4.

Table 2. Norrish-Yang Reactivity of Triketone 5



entry	λ_{\max} (nm)	time (h)	yield ^a of 7 (% brsm)	conversion ^a of 5 (%)
1	254	72	12	57
2	300	72	15	69
3	350	72	n/r	0
4	300 ^b	72	39 ^c	>99
5	254 ^b	72	18	72

^aDetermined by ¹H NMR. ^bReaction was carried out in the presence of 1.0 equiv of benzophenone. ^cIsolated yield.

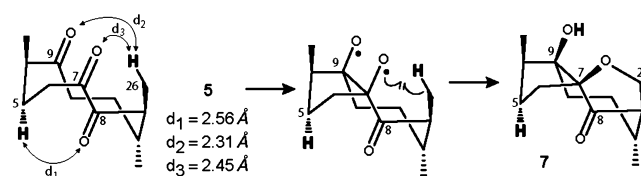


Figure 8. Mechanistic considerations for the formation of 7.

The changing of the light source did not significantly improve the efficiency of this reaction; however, almost complete conversion of the starting material was achieved by the use of benzophenone in combination with a 300 nm UV light (Table 2, entry 4). Low efficiency and long reaction times of the photolyses of triketone 5 are caused, perhaps, by the known reversibility of light-induced pinacolization and hydro-transfer processes.

The relative stereochemistry of 7 was confirmed by NOESY spectroscopy, which showed enhancements between the hydroxyl group at C-9 with H_β-26, H-25, and H_β-12. H_β-12 in turn showed correlations with H-18 and H_β-26, while H_α-26 showed a cross-peak with H_β-16 (Figure 9). These NOESY data have determined the β-facial environment of the newly formed rings B and C.

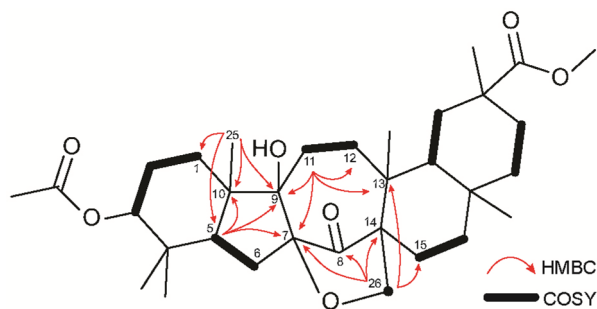


Figure 7. Key HMBC (¹H to ¹³C) and COSY correlations of structure 7.

The formation of structure 7 was not anticipated. Presumably, the initial photoexcitation of the C-7 keto group is followed by a new carbon-carbon bond formation via pinacol-type coupling reaction with the C-9 carbonyl. The resulting oxygen-centered biradical intermediate, formation of which is commonly associated with the photochemical cleavage of cyclic peroxides,^{48–50} undergoes abstraction of ε-hydrogen H-26 by the oxygen of the C-9 carbonyl ($d_2 = 2.31 \text{ \AA}$), followed by a radical cyclization process to form a furan ring (Figure 8).

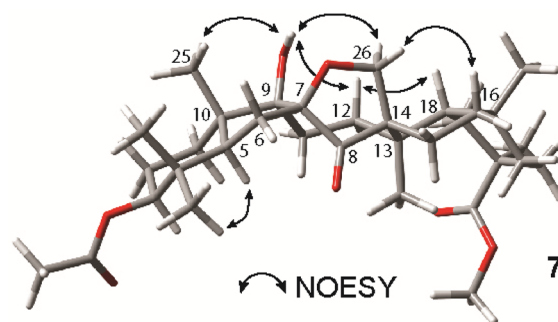


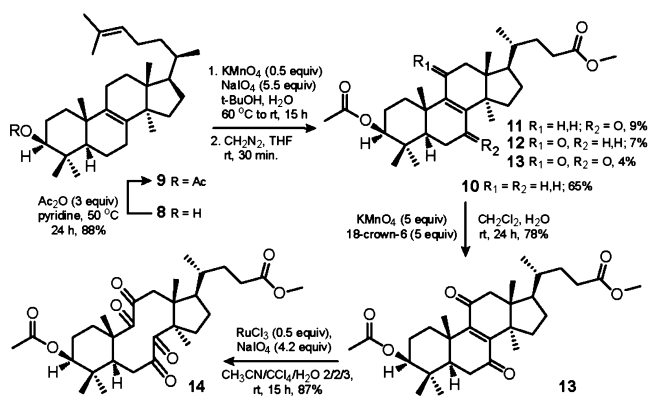
Figure 9. Key NOESY correlations of compound 7.

Having established the reactivity patterns of the polyketones derived from bryonolic acid, we then turned our attention to the tetracyclic triterpenoid lanosterol. We have previously found that the subtle structural differences between bryonolic acid and lanosterol led to dramatic differences in the aldol reactivity of the polyketones derived from these molecules.¹⁸ In this regard, we set out to predict using conformational analysis

and further confirm the possibility of the formation of the alternative product of Yang cyclization via pathway b from lanosterol-derived polyketones **14** and **17**.

The oxidation chemistry leading to tetraketone **14** was next investigated. After initial protection of the hydroxyl group at C-3 of lanosterol **8** to generate acetate **9**, the $\Delta^{24,25}$ double bond of lanosterol acetate **9** was selectively oxidized according to the method developed by Reshetova et al.⁵¹ The use of KMnO_4 and NaIO_4 in aqueous *tert*-BuOH at 60 °C to rt for 15 h, followed by treatment of the resultant carboxylic acids with freshly prepared diazomethane in dry THF for 30 min, gave the desired methyl ester **10** in 65% yield, accompanied by α,β -unsaturated ketones **11** and **12** and enedione **13** in 9, 7, and 4% yield, respectively. It is noteworthy that the formation of α,β -unsaturated ketone **12** was not observed by Reshetova et al. The ester **10** was further oxidized with KMnO_4 and 18-crown-6 in aqueous DCM at rt to furnish enedione **13** in 78% yield after 24 h. Finally, tetraketone **14** was prepared from enedione **13** by catalytic oxidation with ruthenium tetroxide under Sharpless conditions.⁵² The use of RuCl_3 with NaIO_4 as a stoichiometric reoxidant in the mixture of CCl_4 , acetonitrile, and water gave the desired product **14** in 87% yield after 15 h (Scheme 1).

Scheme 1. Sequential Oxidation of $\Delta^{24,25}$ and $\Delta^{8,9}$ of Lanosterol Acetate **9**



A literature search revealed that Marsaioli and co-workers have previously studied the aldol reactivity of a similar tetraketone derived from 24,25-dihydrolanosterol.^{53,54} On the basis of the analysis of ^1H and ^{13}C NMR spectra, the authors have suggested that the tetraketone existed as a mixture of two conformational isomers. Rigorous verification of this suggestion was critical to our analysis and prediction of photochemical behavior of the tetraketone **14**. Therefore, we conducted a variable-temperature NMR study of tetraketone **14**, which indeed was isolated as a mixture of two products (ca. 2.5:1 at 303.15 K), inseparable by various chromatographic means (Figure 10).

^1H signals were assigned by the analysis of COSY, HMQC, and HMBC spectra of tetraketone **14**. ^1H NMR experiments carried out in toluene- d_8 at 0 °C revealed that the H-3 signal exists as a doublet of doublets at 4.82 ppm ($J_1 = 11.4$ Hz, $J_2 = 4.2$ Hz) and a doublet of doublets at 4.60 ppm ($J_1 = 11.4$ Hz, $J_2 = 3.6$ Hz); H-12 splits into two doublets at 3.54 ppm ($J = 13.2$ Hz) and 3.48 ppm ($J = 13.8$ Hz); H-26 shows two singlets at 3.42 and 3.40 ppm, while H-5 appears as a doublet of doublets at 3.21 ppm ($J_1 = J_2 = 3.6$ Hz) and a doublet of doublets at 3.03 ppm ($J_1 = 15.6$ Hz, $J_2 = 9.6$ Hz). With increasing temperature,

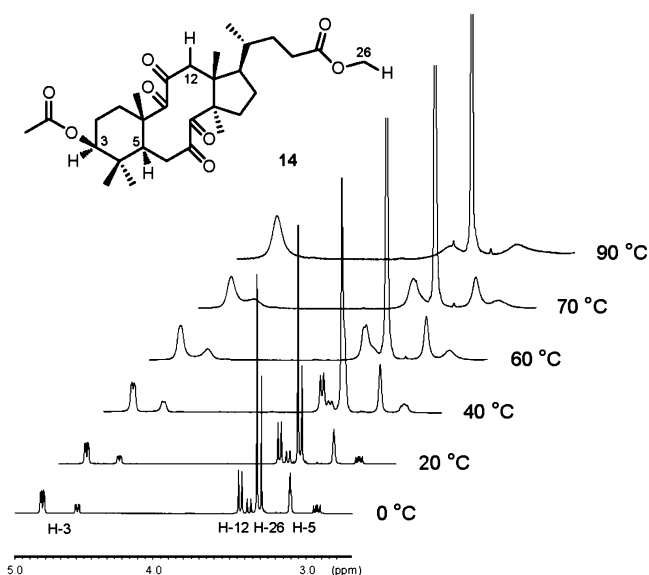


Figure 10. Variable-temperature ^1H NMR study of tetraketone **14**.

all peaks broaden, and at temperatures at and above 80 °C, the doubled peaks merge and only time-average resonances are observed. We argue that the coalescence of the doubled peaks at higher temperatures confirms that tetraketone **14** exists as an equilibrium mixture of two conformational isomers. Lowering the temperature to -30 °C does not lead to any difference in the line shapes, indicating that the conformational equilibrium has reached the slow exchange rate.

On the basis of the empirical calculations using the torsional angles in the 10-membered ring, Marsaioli and co-workers suggested the structures of the four possible conformers of the lanosterol-derived cyclodecatetraone (Figure 11). More accu-

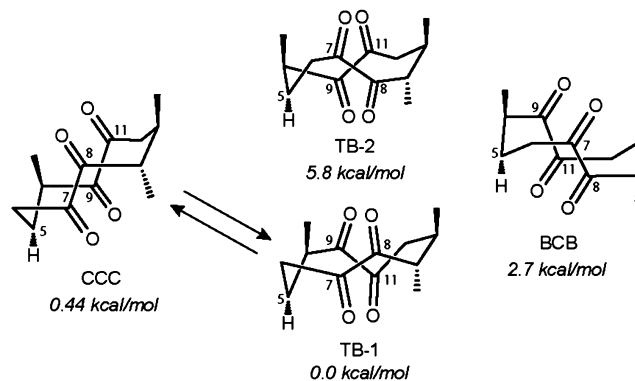


Figure 11. Structures of the possible conformers of tetraketone **14**.

rate energy minimization calculations⁵⁹ of the tetraketone **14** at the B3LYP/6-311G(d,p) level of theory disclosed that the lowest energy conformers CCC (chair–chair–chair) and TB (twist-boat)-1 are almost isoenergetic. Therefore, the energy difference of 0.44 kcal/mol between CCC and TB-1 would correspond well to the equilibrium mixture of two conformers in ca. 2.1:1 ratio at 303.15 K. The assignment of the structures of conformers CCC and TB-1 was further supported by comparison of the experimental J values for H-5 of both conformers with the J values predicted using the dihedral angles of -114° (TB-1, $\text{H}_5\text{H}_{6\alpha}$), 128° (TB-1, $\text{H}_5\text{H}_{6\beta}$), -73° (CCC, $\text{H}_5\text{H}_{6\alpha}$), and 168° (CCC, $\text{H}_5\text{H}_{6\beta}$), which were determined with

the GaussView 3.09 program. Unfortunately, NOESY experiments did not provide definitive evidence as to the structures of the conformers.

Next, we examined the photochemical reactivity of the bichromophoric structure **14**. Analysis of the less populated conformational isomer CCC (Figure 11) revealed that the “bowsprit” γ -hydrogen H-5 is anti-periplanar with C-8 and C-11 keto groups. Disfavorable orientation of reactive functionalities led to a conclusion that CCC must be unreactive in the desired Norrish-Yang photocyclization. On the contrary, examination of the more populated conformer TB-1 revealed that H-5 is antiperiplanar with the π -bond of C-8 carbonyl, but syn-periplanar with the C-11 keto group (Figure 12). Thus,

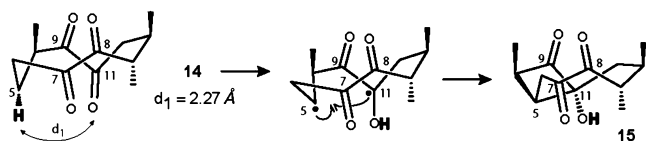
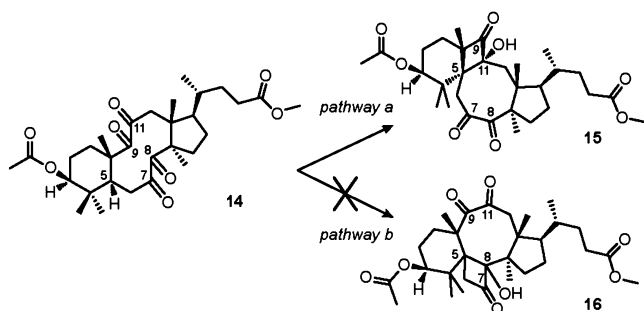


Figure 12. Mechanistic considerations for the formation of cyclobutanol **15**.

favorable spatial position of H-5 and the C-11 carbonyl allowed for the prediction of regiospecific formation of the 1(C-5),4(C-11)-hydroxy biradical, which would be structurally biased to cyclize into *cis*-cyclobutanol **15** via pathway a. In addition, the distance between H-5 and the oxygen of the C-8 carbonyl of TB-1 was determined to be 2.27 Å, increasing the likelihood of the desired reaction. Concomitantly, disfavorable spatial arrangement of H-5 and C8=O should exclude the formation of cyclobutanol **16** via pathway b (Table 3).

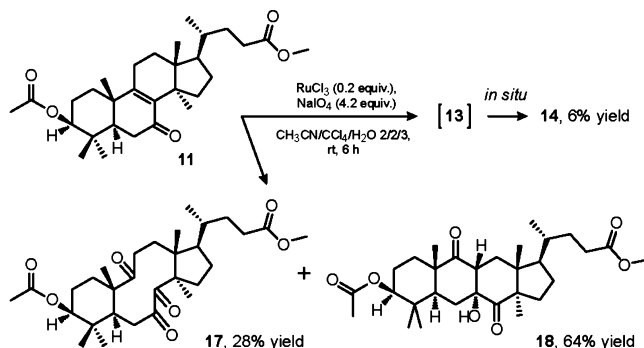
Table 3. Norrish-Yang Reactivity of Tetraketone **14**



unambiguously after comprehensive analysis of 2D NMR experiments and HRMS data (see Supporting Information). It is noteworthy that no other products were observed during the photolysis.

Our attention was then turned toward the oxidation reaction leading to triketone **17** (Scheme 2). In due course, when

Scheme 2. Oxidation of Δ 8,9 of α,β -Unsaturated Ketone **11**



treated with our modified ruthenium conditions, α,β -unsaturated ketone **11** underwent competing cleavage of the Δ 8,9 double bond to give the desired triketone **17** and regioselective allylic oxidation at C-11 to furnish enedione **13**, which was further oxidized in the course of the reaction to yield tetraketone **14** as a minor reaction product. It is noteworthy that the dominating formation of aldol adduct **18** proved to be unavoidable during column chromatography of the crude reaction mixture on silica.

Conformational analysis of triketone **17** revealed that, despite the fact that the keto group at C-8 is in γ -position to H-5, the C-8 carbonyl is anti-periplanar with the C-5-H bond (Figure 13). This observation led to a conclusion that, analogously with

entry	λ_{\max} (nm)	time (h)	yield of 15 (%)	conversion of 14 (%)
1	254	20	48	100
2	300	12	27	100
3	254 ^a	6	72 ^b	60
4	300 ^a	3	66	100

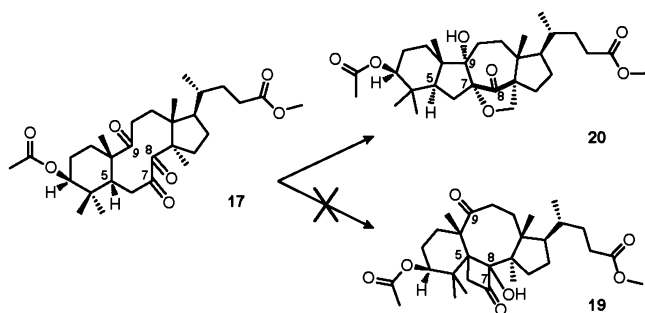
^aReaction was carried out in the presence of 1.0 equiv of benzophenone. ^bYield of **15** is based on the recovered **14**.

In complete agreement with this rationale, irradiation of the solution of tetraketone **14** in dry deoxygenated C_6D_6 in a quartz cuvette with 254 nm UV light led to the formation of the sole product **15** in 48% yield after complete consumption of the starting material in 20 h. The change of the light source to a 300 nm UV lamp led to a shorter reaction time; however, cyclobutanol **15** was isolated in only 27% yield. The addition of 1.0 equiv of benzophenone significantly improved the efficiency of the reaction, affording the highest yield of cyclobutanol **15** (66%, Table 3, entry 4). The structure of **15** was elucidated

the CCC conformer of tetraketone **14**, a prediction can be made that triketone **17** must be unreactive in the desired Norrish-Yang photocyclization and cyclobutanol **19** cannot be formed. However, the possibility of transannular photopinacolization remains plausible for triketone **17**. By direct comparison with triketone **5**, the excitation of the carbonyl at C-7 can be followed by the formation of oxygen-centered biradical. On the basis of the argument of closer spatial proximity, ϵ -hydrogen H-30 may then be abstracted by the oxygen of the C-9 carbonyl (Figure 13, $d_2 = 2.42$ Å), followed by the formation of a furan ring with the oxygen of C-7 carbonyl.

As a result, irradiation of the solution of triketone **17** in dry deoxygenated C_6D_6 in a quartz cuvette with 254 nm UV light for 24 h led to the exclusive formation of furan **20** in 18% isolated yield (41% conversion, Table 4, entry 1), and no other products of the reaction were observed. The change of the λ_{\max} alone did not enhance the efficiency of the reaction; however,

Table 4. Photoreactivity of Triketone 17



entry	λ_{\max} (nm)	time (h)	yield of 20 (% brsm)	conversion of 17 (%)
1	254	24	44	41
2	300	24	19	69
3	300 ^a	24	31	82
4	254 ^a	24	39	55

^aReaction was carried out in the presence of 1.0 equiv of benzophenone.

the use of 1.0 equiv of benzophenone with 300 nm UV light yielded photoproduct 20 in 25% isolated yield (82% conversion, Table 4, entry 3). The structure of furan 20 was confirmed after extensive 2D NMR study and by HRMS data (see Supporting Information).

CONCLUSION

Here we have devised and successfully executed a DOS strategy, whereby the substrates for divergent Norrish-Yang photocyclization were prepared from parent triterpenoids, bryonolic acid and lanosterol, by sequential allylic oxidation and oxidative cleavage reactions. Irradiation of bryonolic acid-derived tetraketone 1 brought a new 6/6/6-fused structural type 4 to the resultant chemical library of triterpenoid analogues by virtue of an unanticipated photopinacolization. The unexpected structure 4 was accompanied by the expected formation of 6/4/8-fused product of Yang cyclization 3 via pathway a. The use of bryonolic acid-derived triketone 5 to force Yang cyclization into pathway b led to predominant pinacol-type coupling reaction to give 6/5/7-fused structure 7, despite the desirable arrangement of the bowsprit H-5 and the keto group at C-8. The subtle differences between the parent triterpenoids resulted in completely different conformational preferences of the polyketones and, concomitantly, completely different spatial orientations of the reactive functionalities. Consequently, Norrish-Yang photocyclization of lanosterol-derived polyketones 14 and 17 via pathway b was proven to be unfeasible, but the pinacol-type coupling reaction of triketone 17 was proven to be predictable. Thus, under our irradiation conditions, tetraketone 14 formed a single photocycloadduct 15 via pathway a, while triketone 17 yielded the anticipated product of photopinacolization 20.

We would argue that these findings constitute a general approach, whereby the identification of substrate-dictated conformational preferences of similar substrates will allow for a reliable prediction of the outcome of Norrish-Yang type II photocyclization, as well as the feasibility of transannular photoinduced pinacol-type coupling reaction. Moreover, we hope that this study will inspire the development of the divergent strategies for the synthesis of polycyclic compounds from other natural product families to screen against different biological targets.

EXPERIMENTAL SECTION

(2*R*,4*aS*,6*aS*,9*aS*,11*S*,13*aS*,16*aS*,16*bR*)-Methyl-11-acetoxy-2,4*a*,6*a*,10,13*a*,16*a*-heptamethyl-7,8,14,15-tetraoxodocosa-hydrobenzo[6,7]cyclodeca[1,2-*a*]naphthalene-2-carboxylate (1). Tetraketone 1 was prepared from bryonolic acid in four steps by a previously published method¹⁸ (74 mg, 14% overall yield). Identity of 1 was confirmed by ¹H and ¹³C NMR. Purity of 1 was determined by ¹H NMR, TLC, and mp. Physical and spectroscopic data were found to match literature¹⁸ data.

General Procedure for Photolyses of Polyketones 1, 5, 14, and 17. A solution of a specified polyketone (20 mg) in dry C₆D₆ (0.6 mL) in a 4 mL rectangular quartz cuvette (0.1 cm × 0.1 cm × 0.4 cm) was deoxygenated by purging with dry argon gas for 15 min while stirring. When specified, benzophenone (1.0 equiv) was added to the reaction mixture. A cuvette was then sealed with a Teflon stopper and placed in the middle of a chamber photoreactor (10 cm distance from the light source), equipped with six UV lamps (8 W each, specified λ_{\max}) and a cooling fan. Solutions were irradiated at rt for a specified amount of time, until specified polyketone was consumed or decomposition was observed, as determined by either TLC or ¹H NMR. After removal of the solvent in vacuo, photoproducts 3, 4, 7, 15, and 20 were isolated by column chromatography on silica with specified ethyl acetate–hexanes mixtures.

Preparation of 3 and 4. Table 1 (entry 1). Following the general procedure for photolyses, the use of tetraketone 1 (0.035 mmol) and 254 nm UV light for 45 min gave 3 (7 mg, 33%) and 4 (2 mg, 10%).

Table 1 (entry 2). Following the general procedure for photolyses, the use of tetraketone 1 (0.035 mmol) and 300 nm UV light for 90 min gave 3 (12.5 mg, 63%) and 4 (2.6 mg, 13%).

Table 1 (entry 3). Following the general procedure for photolyses, the use of tetraketone 1 (0.035 mmol) and 350 nm UV light for 135 min gave 3 (6 mg, 30%) and 4 (1 mg, 5%).

Table 1 (entry 4). Following the general procedure for photolyses, the use of tetraketone 1 (0.035 mmol), benzophenone (6.4 mg, 0.035 mmol), and 300 nm UV light for 45 min gave 3 (11.2 mg, 56%) and 4 (0.1 mg, <1%).

(2*aS*,5*R*,6*aR*,6*bS*,7*aR*,8*aS*,11*S*,12*aR*,15*aS*)-Methyl-11-acetoxy-7*a*-hydroxy-2*a*,5,6*b*,8*a*,12,12,15*a*-heptamethyl-8,14,15-trioxoicosahydro-1*H*-benzo[1',4']cyclobuta[1',2':6,7]cycloocta[1,2-*a*]naphthalene-5-carboxylate (3). Transparent oil. R_f = 0.37 (EA/hex = 3/7). ¹H NMR (600 MHz, CDCl₃, δ): 5.70 (dd, $J_1 = J_2 = 9$ Hz, 1H), 3.60 (s, 3H), 3.40 (d, $J = 12.6$ Hz, 1H), 3.10 (br s, 1H), 2.75 (d, $J = 12.6$ Hz, 1H), 2.35 (d, $J = 16.2$ Hz, 1H), 2.25 (d, $J = 18$ Hz, 1H), 2.17 (ddd, $J_1 = J_2 = 14.4$ Hz, $J_3 = 4.2$ Hz, 1H), 2.02 (s, 3H), 1.73 (d, $J = 18$ Hz, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 0.95 (m, 1H). ¹³C NMR (150 MHz, CDCl₃, δ): 218.9 (CO), 211.5 (CO), 210.0 (CO), 178.7 (CO), 170.4 (CO), 92.2 (COH), 72.4 (CH), 62.3 (C), 56.9 (C), 55.4 (C), 52.4 (CH₃), 47.0 (CH), 43.8 (C), 42.4 (CH₂), 41.2 (CH₂), 40.7 (C), 40.6 (C), 35.4 (CH₂), 33.4 (CH₂), 32.8 (CH₃), 32.7 (C), 31.22 (CH₃), 31.20 (CH₂), 29.8 (CH₂), 29.1 (CH₂), 24.5 (CH₂), 23.2 (CH₂), 22.4 (CH₃), 21.8 (CH₃), 21.6 (CH₃), 21.3 (CH₃), 19.0 (CH₂), 17.2 (CH₃). HRMS (ESI) m/z calcd for C₃₃H₄₈O₈Na⁺ [M + Na]⁺ 595.3247, found 595.3236.

(2*R*,4*aS*,6*aS*,7*aS*,8*aR*,10*S*,12*aS*,13*aR*,14*aS*,14*bR*)-Methyl-10-acetoxy-7*a*-hydroxy-2,4*a*,6*a*,9,9,12*a*,14*a*-heptamethyl-7,13-dioxoicosahydro-8*a*,13*a*-epoxybenzo[*a*]tetracene-2-carboxylate (4). Transparent oil. R_f = 0.32 (EA/hex = 3/7). ¹H NMR (600 MHz, CDCl₃, δ): 4.81 (dd, $J_1 = 10.8$ Hz, $J_2 = 4.8$ Hz, 1H), 3.61 (s, 3H), 2.69 (d, $J = 14.4$ Hz, 1H), 2.36 (d, 15 Hz, 1H), 2.05 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.19 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H), 0.77 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, δ): 212.6 (CO), 212.4 (CO), 178.6 (CO), 170.6 (CO), 90.6 (C), 90.3 (C), 77.3 (C), 76.5 (CH), 52.7 (C), 51.6 (CH₃), 48.7 (C), 44.3 (CH), 40.4 (C), 40.4 (C), 39.8 (CH₂), 38.5 (C), 35.4 (CH₂), 33.9 (CH₂), 32.5 (CH₃), 31.5 (CH₃), 31.3 (C), 31.1 (CH₂), 30.7 (CH₂), 29.91 (CH₂), 29.87 (CH₂), 24.2 (CH₂), 23.1 (CH₂), 22.3 (CH₃), 21.4 (CH₃), 20.8 (CH₃), 19.4 (CH₃), 18.5 (CH₃), 17.7 (CH₃). HRMS (ESI) m/z calcd for C₃₃H₄₈O₈Na⁺ [M + Na]⁺ 595.32414, found 595.32423.

(*2R,4aS,6aS,9aS,11S,13aS,16aS,16bR*)-Methyl-11-acetoxy-2,4a,6a,10,10,13a,16a-heptamethyl-7,8,14-trioxodocosa-hydrobenzo[6,7]cyclodeca[1,2-*a*]naphthalene-2-carboxylate (**5**). Triketone **5** was prepared from bryonolic acid in three steps by a previously published method¹⁸ (184 mg, 23% overall yield). Identity of **5** was confirmed by ¹H and ¹³C NMR and HRMS. Purity of **5** was determined by ¹H NMR, TLC, and mp. Physical and spectroscopic data were found to match literature¹⁸ data.

Preparation of 7. Table 2 (entry 1). Following the general procedure for photolyses, the use of triketone **5** (0.036 mmol) and 254 nm UV light for 72 h yielded an inseparable mixture (10 mg) of **7** (1.4 mg, 12% brsm, determined by ¹H NMR) and unreacted **5** (8.6 mg, 57% conversion, determined by ¹H NMR). *R_f* = 0.4 (EA/hex = 3/7).

Table 2 (entry 2). Following the general procedure for photolyses, the use of triketone **5** (0.036 mmol) and 300 nm UV light for 72 h yielded an inseparable mixture (8.3 mg) of **7** (2.1 mg, 15% brsm, determined by ¹H NMR) and unreacted **5** (6.2 mg, 69% conversion, determined by ¹H NMR). *R_f* = 0.4 (EA/hex = 3/7).

Table 2 (entry 3). Following the general procedure for photolyses, the use of triketone **5** (0.036 mmol) and 350 nm UV light for 72 h yielded unreacted **5** (20 mg, 0% conversion). *R_f* = 0.4 (EA/hex = 3/7).

Table 2 (entry 4). Following the general procedure for photolyses, the use of triketone **5** (0.036 mmol), benzophenone (6.5 mg, 0.036 mmol), and 300 nm UV light for 72 h yielded **7** (7.8 mg, 39%). *R_f* = 0.4 (EA/hex = 3/7).

Table 2 (entry 5). Following the general procedure for photolyses, the use of triketone **5** (0.036 mmol), benzophenone (6.5 mg, 0.036 mmol), and 254 nm UV light for 72 h yielded an inseparable mixture (8.2 mg) of **7** (2.5 mg, 18% brsm, determined by ¹H NMR) and unreacted **5** (5.7 mg, 72% conversion, determined by ¹H NMR). *R_f* = 0.4 (EA/hex = 3/7).

(*2R,4aS,6aS,8aS,9aS,11S,13aS,13bR,15aS,15bR*)-Methyl-11-acetoxy-13b-hydroxy-2,4a,10,10,13a,15a-hexamethyl-16-oxocosa-hydro-6a,8a-methanoindeno[2,1-*b*]naphtho[1,2-*f*]oxocine-2-carboxylate (**7**). Analytically pure **7** was obtained by the following procedure. A round-bottom flask open to atmosphere was charged with basic alumina (365 mg, 3.58 mmol), followed by the addition of DCM (0.5 mL). A mixture (20 mg), containing **5** (17.2 mg, 0.031 mmol) and **7** (2.8 mg, 5 μmol) as determined by ¹H NMR, was dissolved in DCM (0.5 mL) and subsequently added to the resulting suspension. The flask was sealed with a glass stopper and vigorously stirred at rt overnight, at which time the suspension was filtered over a fine sinter funnel and washed successively with ethyl acetate. After removal of the solvent in vacuo, the column chromatography on silica yielded **7** as a transparent oil (2 mg, 71% recovery). *R_f* = 0.38 (EA/hex = 25/75). ¹H NMR (600 MHz, CDCl₃, δ): 4.51 (dd, *J*₁ = 11.4 Hz, *J*₂ = 4.2 Hz, 1H), 4.29 (d, *J* = 9.6 Hz, 1H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.64 (s, 3H), 3.07 (br s, 1H), 2.05 (s, 3H), 1.19 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.85 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, δ): 212.9 (CO), 179.3 (CO), 171.1 (CO), 87.3 (C), 80.5 (CH), 78.9 (C), 72.6 (CH₂), 53.9 (C), 52.0 (CH₃), 48.3 (CH), 47.4 (C), 46.7 (CH), 40.7 (C), 39.7 (C), 37.3 (C), 36.8 (CH₂), 34.0 (CH₂), 33.5 (CH₂), 32.2 (CH₂), 31.8 (C), 31.3 (CH₃), 30.96 (CH₂), 30.90 (CH₃), 29.3 (CH₂), 29.2 (CH₂), 29.1 (CH₃), 29.0 (CH₂), 25.6 (CH₂), 25.3 (CH₂), 21.4 (CH₃), 17.5 (CH₃), 17.2 (CH₃), 16.6 (CH₃). HRMS (ESI) *m/z* calcd for C₃₃H₅₀O₇Na⁺ [*M* + Na]⁺ 581.34488, found 581.34503. The starting material **5** reacted with basic alumina to give the corresponding product of aldol addition. This product of aldol addition retained on silica during column chromatography due to the presence of the hydroxyl group and was not isolated. The synthesis, purification, and structural analysis of the product of aldol addition of **5** were previously studied by our group.¹⁸

(*3S,5R,10S,13R,14R,17R*)-4,4,10,13,14-Pentamethyl-17-((*R*)-6-methylhept-5-en-2-yl)-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (**9**). In a round-bottom flask, lanosterol **8** (10g, 23.4 mmol; 60% in the mixture with 24,25-dihydrolanosterol, purchased from various commercial sources) and DMAP (143 mg, 1.17 mmol) were dissolved in 47 mL of dry pyridine. Acetic anhydride (7.18 g, 70.3 mmol, 6.6 mL) was added to the resulting solution by a quick syringe transfer.

The reaction mixture was stirred at 50 °C overnight, after which time pyridine was removed at reduced pressure and the crude mixture was taken up in DCM. The organic layer was washed successively with dilute HCl, saturated solution of sodium bicarbonate, and brine. It was subsequently dried over Na₂SO₄ and the solvent removed in vacuo. The crude product was purified by column chromatography to give **9** (60% in the mixture with 24,25-dihydrolanosterol acetate) as a white solid (9.7 g, 88%). *R_f* = 0.55 (EA/hex = 10/90). Identity and purity of **9** were confirmed by ¹H and ¹³C NMR. Spectroscopic data were found to match literature⁵⁵ data.

Preparation of 10–13. Using a modified literature protocol,⁵¹ lanosterol acetate **9** (10 g, 60% in the mixture with 24,25-dihydrolanosterol acetate, 12.8 mmol) was dissolved in 1 L of *tert*-BuOH at 60 °C, followed by the addition of K₂CO₃ (10g, 72.4 mmol). Meanwhile, a solution of KMnO₄ (1.42 g, 9 mmol) and NaIO₄ (24.1 g, 0.113 mol) in 800 mL of H₂O was heated to 60 °C and subsequently added to the resulting suspension in one portion. The flask was removed from heat, and the reaction mixture was allowed to cool to rt and stirred at rt overnight, at which time the reaction was interrupted by the addition of saturated solution of sodium thiosulfate until complete discoloration was observed (about 250 mL). After the organic layer was separated and the solvent removed in vacuo, the crude residue was acidified with dilute HCl and extracted with DCM. The organic layer was washed successively with water and brine. It was subsequently dried over Na₂SO₄ and the solvent removed in vacuo. The crude mixture of products was separated by gradient elution column chromatography on silica with ethyl acetate–hexanes mixtures. The use of hexanes as an eluting solvent yielded pure 24,25-dihydrolanosterol acetate as a white solid (3.36 g, 84%). *R_f* = 0.75 (EA/hex = 20/80). Mp: 118–120 °C (lit.⁵⁶ mp 120–121 °C). Elution with progressively more polar combinations of eluting solvent, followed by the use of ethyl acetate as an eluting solvent, gave a crude mixture (6.5 g) of carboxylic acids. In a round-bottom flask open to atmosphere, the mixture of carboxylic acids (6.5 g) was dissolved in 50 mL of freshly distilled THF. Freshly prepared diazomethane in diethyl ether (15 mmol) was added dropwise to the resulting solution by a pipet, and the reaction mixture was stirred at rt until full conversion was detected by TLC (approximately 30 min). The reaction was quenched by dropwise addition of glacial acetic acid until the yellow color of the solution disappeared. The solvent was removed in vacuo, and the crude mixture of products was separated by careful column chromatography on silica to yield **10** as a white solid (3.9 g, 65%), **11** as a white solid (610 mg, 9%), **12** as a white solid (420 mg, 7%), and **13** as a yellow solid (270 mg, 4%).

(*R*)-Methyl-4-((*3S,5R,10S,13R,14R,17R*)-3-acetoxy-4,4,10,13,14-pentamethyl-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-pentanoate (**10**). Mp: 174–177 °C (lit.⁵¹ mp 226–227 °C, lit.⁵⁷ mp 174–176 °C). *R_f* = 0.58 (EA/hex = 20/80). Identity and purity of **10** were confirmed by ¹H and ¹³C NMR, HRMS, and TLC. Spectroscopic data did not duplicate literature⁵¹ data. ¹H NMR (400 MHz, CDCl₃, δ): 4.50 (dd, *J*₁ = 11.6 Hz, *J*₂ = 4.4 Hz, 1H), 3.66 (s, 3H), 2.37 (m, 1H), 2.22 (m, 1H), 2.05 (s, 3H), 1.00 (s, 3H), 0.89 (d, *J* = 6 Hz, 3H), 0.88 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.68 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, δ): 174.9, 171.1, 134.6, 134.4, 81.1, 51.6, 50.6, 50.4, 50.0, 44.7, 38.0, 37.0, 36.2, 35.4, 31.41, 31.39, 31.1, 30.9, 28.2, 28.1, 26.5, 24.4, 24.3, 21.5, 21.1, 19.3, 18.4, 18.3, 16.7, 15.9. HRMS (ESI) *m/z* calcd for C₃₀H₄₈O₄Na⁺ [*M* + Na]⁺ 495.34448, found 495.34456.

(*R*)-Methyl-4-((*3S,5R,10S,13R,14R,17R*)-3-acetoxy-4,4,10,13,14-pentamethyl-7-oxo-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (**11**). Mp: 200–203 °C (lit.⁵¹ mp 255–258 °C). *R_f* = 0.28 (EA/hex = 20/80). *R_f* = 0.39 (EA/hex = 25/75). Identity of **11** was confirmed by ¹H and ¹³C NMR and HRMS. Purity of **11** was determined by ¹H NMR and TLC. ¹H NMR data did not duplicate literature⁵¹ data. ¹³C NMR data were not reported in chemical literature. ¹H NMR (600 MHz, CDCl₃, δ): 4.52 (dd, *J*₁ = 11.6 Hz, *J*₂ = 4.4 Hz, 1H), 3.66 (s, 3H), 2.06 (s, 3H), 1.18 (s, 3H), 0.95 (s, 3H), 0.91 (m, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.65 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, δ): 198.8 (CO), 174.8 (CO), 171.0

(CO), 164.7 (C), 139.1 (C), 79.7 (CH), 51.6 (CH₃), 50.0 (CH), 48.9 (CH), 47.9 (C), 45.1 (C), 39.8 (C), 37.9 (C), 36.6 (CH₂), 36.1 (CH), 34.6 (CH₂), 32.1 (CH₂), 31.4 (CH₂), 31.4 (CH₂), 30.2 (CH₂), 28.8 (CH₂), 27.5 (CH₃), 25.1 (CH₃), 24.0 (CH₂), 23.8 (CH₂), 21.4 (CH₃), 18.6 (CH₃), 18.5 (CH₃), 16.5 (CH₃), 15.9 (CH₃). HRMS (ESI) *m/z* calcd for C₃₀H₄₇O₅⁺ [M + H]⁺ 487.34180, found 487.34188.

(R)-Methyl-4-((3S,5R,10S,13R,14R,17R)-3-acetoxy-4,4,10,13,14-pentamethyl-11-oxo-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (12). Mp: 144–147 °C (lit.⁵⁷ mp 145–149 °C). *R_f* = 0.33 (EA/hex = 20/80). *R_f* = 0.42 (EA/hex = 25/75). Identity of **12** was confirmed by ¹H and ¹³C NMR and HRMS. Purity of **12** was determined by ¹H NMR, TLC, and mp. Spectroscopic data for **12** were not previously reported. ¹H NMR (600 MHz, CDCl₃, δ): 4.49 (dd, *J*₁ = 10.2 Hz, *J*₂ = 6 Hz, 1H), 3.65 (s, 3H), 2.99 (ddd, *J*₁ = 13.8 Hz, *J*₂ = *J*₃ = 3.6 Hz, 1H), 2.64 (d, *J* = 16.2 Hz, 1H), 2.44 (d, *J* = 16.2 Hz, 1H), 2.03 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H), 0.88 (s, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.80 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, δ): 199.1 (CO), 174.6 (CO), 171.1 (CO), 164.2 (C), 139.5 (C), 80.7 (CH), 52.0 (CH), 51.9 (CH₂), 51.7 (CH₃), 51.6 (C), 50.1 (CH), 47.4 (C), 38.0 (C), 37.6 (C), 35.8 (CH), 34.1 (CH₂), 31.2 (CH₂), 31.0 (CH₂), 31.0 (CH₂), 29.9 (CH₂), 28.4 (CH₃), 27.0 (CH₂), 25.9 (CH₃), 24.3 (CH₂), 21.4 (CH₃), 19.1 (CH₃), 18.1 (CH₃), 17.3 (CH₂), 16.9 (CH₃), 16.8 (CH₂). HRMS (ESI) *m/z* calcd for C₃₀H₄₇O₅⁺ [M + H]⁺ 487.3423, found 487.3426.

(R)-Methyl-4-((3S,5R,10S,13R,14R,17R)-3-acetoxy-4,4,10,13,14-pentamethyl-7,11-dioxo-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (13). A 100 mL round-bottom flask open to atmosphere was charged with KMnO₄ (2.67 g, 16.92 mmol) and 18-crown-6 (4.47 g, 16.92 mmol), followed by the addition of 33.9 mL of water. A solution of **10** (1.6 g, 3.385 mmol) in 33.9 mL of DCM was then added to the resulting suspension by a quick syringe transfer. The flask was sealed with a glass stopper, and the reaction mixture was vigorously stirred at rt for 24 h, at which time the mixture was filtered over a fine sinter funnel and washed with DCM. Layers were separated, and the aqueous layer was extracted with DCM. The organic layer was dried over Na₂SO₄ and the solvent removed in vacuo. The crude product was purified by column chromatography on silica to give **13** as a yellow solid (1.32 g, 78%). Mp: 142–145 °C (lit.⁵¹ mp 178–179 °C, lit.⁵⁸ mp 141–143 °C). *R_f* = 0.25 (EA/hex = 20/80). *R_f* = 0.37 (EA/hex = 25/75). Identity of **13** was confirmed by ¹H and ¹³C NMR and HRMS. Purity of **13** was determined by ¹H NMR, TLC, and mp. ¹³C NMR data was found to match literature⁵¹ data. ¹H NMR data did not duplicate literature^{51,58} data. ¹H NMR (400 MHz, CDCl₃, δ): 4.51 (dd, *J*₁ = 11.2 Hz, *J*₂ = 5.2 Hz, 1H), 3.65 (s, 3H), 2.88 (ddd, *J*₁ = 13.6 Hz, *J*₂ = *J*₃ = 3.6 Hz, 1H), 2.75 (d, *J* = 16 Hz, 1H), 2.58 (d, *J* = 16 Hz, 1H), 2.04 (s, 3H), 1.31 (s, 3H), 1.15 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H), 0.87 (d, *J* = 5.2 Hz, 3H), 0.78 (s, 3H). HRMS (ESI) *m/z* calcd for C₃₀H₄₅O₆⁺ [M + H]⁺ 501.32107, found 501.32111.

(R)-Methyl-4-((1R,3aR,6aS,8S,10aS,13aR)-8-acetoxy-3a,7,7,10a,13a-pentamethyl-4,5,11,12-tetraoxohexadecahydro-1H-benzo[a]cyclopenta[f][10]annulen-1-yl)pentanoate (14). Using modified literature protocol,⁵⁴ RuCl₃ (62 mg, 0.299 mmol) was added in one portion to the solution of NaIO₄ (539 mg, 2.52 mmol) in 18 mL of water, and the resulting suspension was stirred open to atmosphere for 15 min, followed by the addition of 12 mL of acetonitrile. The solution of **13** (300 mg, 0.599 mmol) in 12 mL of CCl₄ was then added to the reaction mixture by a quick syringe transfer. The flask was sealed with a glass stopper, and the resulting biphasic mixture was vigorously stirred at rt for 15 h, at which time the reaction was interrupted by the addition of 5 mL of ethanol. The layers were separated, and the aqueous layer was extracted with DCM. The organic layer was dried over Na₂SO₄ and the solvent removed in vacuo. The crude product was purified by column chromatography on silica to give **14** as a yellow solid (278 mg, 87%). Mp: 140–143 °C. *R_f* = 0.39 (EA/hex = 25/75). ¹H NMR (600 MHz, toluene-*d*₈, 273.15 K, δ) major conformer: 4.82 (dd, *J*₁ = 11.4 Hz, *J*₂ = 4.2 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.42 (s, 3H), 3.21 (dd, *J*₁ = *J*₂ = 3.6 Hz, 1H), 2.69 (ddd, *J*₁ = *J*₂ = 12.6 Hz, *J*₃ = 6.6 Hz, 1H), 1.67 (s, 3H), 1.34 (s, 3H),

1.01 (s, 3H), 0.98 (s, 3H), 0.75 (s, 3H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.64 (s, 3H). Minor conformer: 4.60 (dd, *J*₁ = 11.4 Hz, *J*₂ = 3.6 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 1H), 3.40 (s, 3H), 3.03 (dd, *J*₁ = 15.6 Hz, *J*₂ = 9.6 Hz, 1H), 1.65 (s, 3H), 1.42 (s, 3H), 1.30 (s, 3H), 0.87 (s, 3H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.63 (s, 3H). ¹³C NMR (150 MHz, toluene-*d*₈, 273.15 K, δ) major conformer: 208.7, 206.1, 205.1, 203.2, 173.7, 169.8, 79.6, 62.3, 55.1, 53.1, 51.5, 49.7, 48.2, 44.3, 38.9, 37.6, 36.3, 33.8, 31.7, 31.61, 31.59, 30.9, 28.6, 24.3, 23.9, 20.3, 20.2, 19.6, 17.9, 16.5. Minor conformer: 207.3, 207.1, 202.6, 201.3, 173.3, 169.2, 78.7, 60.6, 52.3, 50.98, 50.0, 49.4, 46.9, 41.4, 38.7, 35.6, 35.2, 34.8, 34.5, 30.7, 27.3, 24.4, 22.7, 19.64, 18.9, 17.8, 17.0, 16.2. HRMS (ESI) *m/z* calcd for C₃₀H₄₄O₈Na⁺ [M + Na]⁺ 555.29284, found 555.29296.

Preparation of 15. Table 3 (entry 1). Following the general procedure for photolyses, the use of tetraketone **14** (0.0375 mmol) and 254 nm UV light for 20 h yielded **15** (9.6 mg, 48%).

Table 3 (entry 2). Following the general procedure for photolyses, the use of tetraketone **14** (0.0375 mmol) and 300 nm UV light for 12 h yielded **15** (5.3 mg, 27%).

Table 3 (entry 3). Following the general procedure for photolyses, the use of tetraketone **14** (0.0375 mmol), benzophenone (6.8 mg, 0.0375 mmol), and 254 nm UV light for 6 h yielded unreacted **14** (8.1 mg, 60% conversion) and **15** (8.6 mg, 72% brsm).

Table 3 (entry 4). Following the general procedure for photolyses, the use of tetraketone **14** (0.0375 mmol), benzophenone (6.8 mg, 0.0375 mmol), and 300 nm UV light for 3 h yielded **15** (13.1 mg, 66%).

(R)-Methyl-4-((1aS,4S,5aR,8aR,11R,11aR,12aR)-4-acetoxy-12a-hydroxy-1a,5,5,8a,11a-pentamethyl-1,7,8-trioxo-hexadecahydrobenzo[1,4]cyclobuta[1,2-*a*]cyclopenta[*d*][8]-annulen-11-yl)pentanoate (15). Transparent oil. *R_f* = 0.25 (EA/hex = 25/75). ¹H NMR (400 MHz, CDCl₃, δ): 5.65 (m, 1H), 3.69 (s, 3H), 2.90 (d, *J* = 13.9 Hz, 1H), 2.83 (br s, 1H), 2.60 (d, *J* = 13.9 Hz, 1H), 2.07 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H), 1.16 (s, 3H), 1.16 (s, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.93 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, δ): 213.3 (CO), 210.0 (CO), 209.5 (CO), 174.3 (CO), 171.3 (CO), 94.9 (C), 78.7 (CH), 63.4 (C), 59.5 (C), 56.2 (C), 53.9 (CH), 51.8 (CH₃), 47.8 (C), 43.1 (CH₂), 40.9 (CH₂), 40.0 (C), 35.6 (CH₂), 34.2 (CH), 31.9 (CH₂), 30.9 (CH₂), 29.3 (CH₂), 23.0 (CH₂), 22.7 (CH₂), 21.6 (CH₃), 21.4 (CH₃), 20.5 (CH₃), 20.3 (CH₃), 19.8 (CH₃), 19.5 (CH₂), 17.7 (CH₃). HRMS (ESI) *m/z* calcd for C₃₀H₄₄O₈Na⁺ [M + Na]⁺ 555.2934, found 555.2933.

Preparation of 17 and 18. In a 100 mL single-neck round-bottom flask, RuCl₃ (30 mg, 0.144 mmol) was added in one portion to a solution of NaIO₄ (646 mg, 3.02 mmol) in 22 mL of H₂O, and the resulting suspension was stirred open to atmosphere for 15 min, followed by the addition of 14.5 mL of acetonitrile. The solution of **11** (350 mg, 0.719 mmol) in 14.5 mL of CCl₄ was then added dropwise to the reaction mixture by a syringe pump. The flask was sealed with a glass stopper, and the resulting biphasic mixture was vigorously stirred for 6 h, at which time 3 mL of ethanol was added to the solution. The layers were separated, and the aqueous layer was extracted with DCM. The organic layer was dried over Na₂SO₄, concentrated under vacuum, and the crude mixture of products was further separated by column chromatography on silica to yield tetraketone **14** as a yellow solid (24 mg, 6%), *R_f* = 0.39 (EA/hex = 25/75), triketone **17** as a yellow oil (103 mg, 28%), and aldol adduct **18** as a white solid (238 mg, 64%).

(R)-Methyl 4-((1R,3aR,6aS,8S,10aS,13aR)-8-acetoxy-3a,7,7,10a,13a-pentamethyl-4,5,11-trioxohexadecahydro-1H-benzo[a]cyclopenta[f][10]annulen-1-yl)pentanoate (17). *R_f* = 0.26 (EA/hex = 25/75). ¹H NMR (400 MHz, CDCl₃, δ): 4.66 (dd, *J*₁ = 11.6 Hz, *J*₂ = 4.4 Hz, 1H), 3.67 (s, 3H), 2.81 (dd, *J*₁ = 16.4 Hz, *J*₂ = 7.6 Hz, 1H), 2.06 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 0.98 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 3H), 0.79 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, δ): 214.0, 209.2, 203.2, 174.4, 170.7, 79.4, 59.0, 53.4, 53.1, 52.2, 51.7, 50.4, 39.2, 36.2, 35.5, 34.3, 33.8, 33.2, 31.7, 30.8, 28.0, 26.1, 25.1, 23.4, 21.3, 20.3, 19.4, 17.7, 17.3, 16.8. HRMS (ESI) *m/z* calcd for C₃₀H₄₇O₇⁺ [M + H]⁺ 519.33163, found 519.33173.

(R)-Methyl-4-((1R,3aR,4aR,5aS,7S,9aS,10aR,11aR)-7-acetoxy-4a-hydroxy-3a,6,6,9a,11a-pentamethyl-4,10-dioxohexadecahydro-1H-cyclopenta[*b*]anthracen-1-yl)pentanoate (18). Mp:

260–264 °C. $R_f = 0.15$ (EA/hex = 25/75). ^1H NMR (600 MHz, CDCl_3 , δ): 4.48 (dd, $J_1 = 11.4$ Hz, $J_2 = 4.6$ Hz, 1H), 3.65 (s, 3H), 3.10 (dd, $J_1 = 12.4$ Hz, $J_2 = 2.6$ Hz, 1H), 2.13 (d, $J = 13.3$ Hz, 1H), 2.04 (s, 3H), 1.28 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.95 (d, $J = 6.4$ Hz, 3H), 0.88 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3 , δ): 211.8 (CO), 211.6 (CO), 174.6 (CO), 171.0 (CO), 80.0 (CH), 79.2 (C), 59.3 (C), 51.7 (CH₃), 50.2 (CH), 49.5 (CH), 47.9 (C), 47.3 (C), 45.5 (CH), 38.5 (C), 35.3 (CH), 31.2 (CH₂), 31.1 (CH₂), 30.7 (CH₂), 29.3 (CH₂), 28.9 (CH₂), 28.4 (CH₂), 28.1 (CH₃), 26.9 (CH₂), 23.6 (CH₂), 22.8 (CH₃), 21.3 (CH₃), 19.5 (CH₃), 18.7 (CH₃), 18.6 (CH₃), 17.3 (CH₃). HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{46}\text{O}_7\text{Na}^+$ [$\text{M} + \text{Na}$]⁺ 541.31357, found 541.31373.

Preparation of 20. Table 4 (entry 1). Following the general procedure for photolyses, the use of triketone 17 (0.0386 mmol) and 254 nm UV light for 24 h yielded unreacted 17 (11.8 mg, 41% conversion) and 20 (3.6 mg, 44% brsm).

Table 4 (entry 2). Following the general procedure for photolyses, the use of triketone 17 (0.0386 mmol) and 300 nm UV light for 24 h yielded unreacted 17 (6.3 mg, 69% conversion) and 20 (2.6 mg, 19% brsm).

Table 4 (entry 3). Following the general procedure for photolyses, the use of triketone 17 (0.0386 mmol), benzophenone (7 mg, 0.0386 mmol), and 300 nm UV light for 24 h yielded unreacted 17 (3.7 mg, 82% conversion) and 20 (5 mg, 31% brsm).

Table 4 (entry 4). Following the general procedure for photolyses, the use of triketone 17 (0.0386 mmol), benzophenone (7 mg, 0.0386 mmol), and 254 nm UV light for 24 h yielded unreacted 17 (9 mg, 55% conversion) and 20 (4.3 mg, 39% brsm).

(R)-Methyl-4-((1R,3aR,5aR,6aS,8S,10aS,10bS,12aR)-8-ace-toxy-10b-hydroxy-7,7,10a,12a-tetramethyl-13-oxotetra-decahydro-1H-3a,5a-methanocyclopenta[*f*]indeno[2,1-*b*]-oxocin-1-yl)pentanoate (20). Transparent oil. $R_f = 0.23$ (EA/hex = 25/75). ^1H NMR (600 MHz, CDCl_3 , δ): 4.56 (dd, $J_1 = 11.9$ Hz, $J_2 = 4.7$ Hz, 1H), 4.26 (d, $J = 9.3$ Hz, 1H), 3.80 (d, $J = 9.3$ Hz, 1H), 3.66 (s, 3H), 3.63 (s, 1H), 2.05 (s, 3H), 0.96 (s, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3 , δ): 209.9 (CO), 174.5 (CO), 171.1 (CO), 89.5 (C), 80.89 (CH), 80.88 (C), 74.1 (CH₂), 61.4 (C), 53.5 (CH), 51.7 (CH₃), 49.9 (C), 49.2 (CH), 49.1 (C), 37.0 (C), 34.8 (CH), 31.3 (CH₂), 31.2 (CH₂), 30.4 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.4 (CH₃), 27.4 (CH₂), 26.2 (CH₂), 24.4 (CH₂), 21.4 (CH₃), 19.0 (CH₃), 16.8 (CH₃), 15.4 (CH₃), 15.3 (CH₃). HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{46}\text{O}_7\text{Na}^+$ [$\text{M} + \text{Na}$]⁺ 541.3141, found 541.3142.

■ ASSOCIATED CONTENT

📄 Supporting Information

General experimental details, complete ref S9, conformational analyses of 14 and 17, ^{13}C VT NMR of 14, atomic coordinates for the optimized geometry for 1, 5, 14, 17; copies of ^1H and ^{13}C NMR spectra of all new compounds, as well as all known compounds that were prepared by new or modified synthetic protocols; copies of HMQC, HMBC, COSY, and NOESY NMR spectra, as well as tables of ^1H and ^{13}C peak assignments and HMQC correlations of 3, 4, 7, 11, 12, 15, 18, 20; key COSY, HMBC, and NOESY correlations of compounds 11, 12, 15, 18, 20. 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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- (59) All computational work described herein was carried out using Gaussian 09, revision A.02 (see Supporting Information for full reference).