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Direct Access to 6/5/7/5- and 6/7/5/5-Fused Tetracyclic Triterpenoids via Divergent Transannular Aldol Reaction of Lanosterol-Derived Diketone

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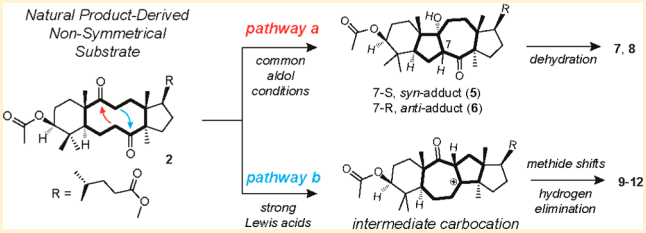
Supporting Information

ABSTRACT: In an effort to access biologically relevant chemical space, a complex natural product derived nonsymmetrical diketone was prepared as a substrate for divergent transannular aldol reactions. The use of common aldol conditions resulted in predominant *syn*-addition via pathway a, while the use of alumina provided access to the *anti*-adduct. Screening of a range of Lewis acids of varying strength unexpectedly resulted in the formation of aldol products with 6/7/5/5-fused molecular skeleton via pathway b.



The remodeling of the core skeletal framework of natural products stands at the forefront of contemporary medicinal chemistry.[1−7] Steroidal natural products possess a multitude of bioactivities and, therefore, constitute an attractive target for combinatorial chemistry[8] and diversity-oriented synthesis (DOS).[9,10] Steroids play many physiologically important roles: the bile acids, sex hormones, cholesterol, and D vitamins are biosynthesized from a single precursor, lanosterol, via the mevalonate pathway.[11] Furthermore, unsaturated B/C ring fusion makes lanosterol a valuable starting point for the creation of markedly different steroid-derived scaffolds. Specifically, this reactive functionality can be manipulated to convert the parent molecule into a pseudosymmetrical diketone. Such a diketone comprises a perfect substrate for divergent aldol reaction, potentially leading to 6/5/7/5- and 6/7/5/5-fused molecular skeletons via pathways a and b, respectively.

The aldol reaction of nonsymmetrical substrates to form both possible products has historically proven difficult.[12−15] With respect to lanosterol-derived diketone, Snatzke[16−18] in his earlier work predicted the unfeasibility of the formation of the aldol product via pathway b due to the presence of a strained trans-fused bicyclo[3.3.0]octane fragment in this product. Using this knowledge, Jagodzinski and Sicinski[19,20] have devised an efficient four-step synthetic route leading to a molecular skeleton with the desired ring-fusion type. Concurrently, Fox and Scott[21] have treated the diketone with neutral alumina to obtain two epimeric aldol adducts via pathway a, although the stereochemistry of these products was not investigated (Figure 1).

Given the fact that stereochemical diversity is another key aspect in the construction of chemical libraries,[22,23] we initiated the research described herein to (1) identify and further reinforce the substrate-dictated diastereoselectivity of the aldol addition of a lanosterol-derived diketone via pathway a and (2) explore the possibility of overturning this substrate-biased stereoselectivity by a thoughtful reagent choice. The central premise behind our study was to use the inherent complexity of the natural product-derived substrate as a stereocontrolling element for transannular aldol addition reaction.

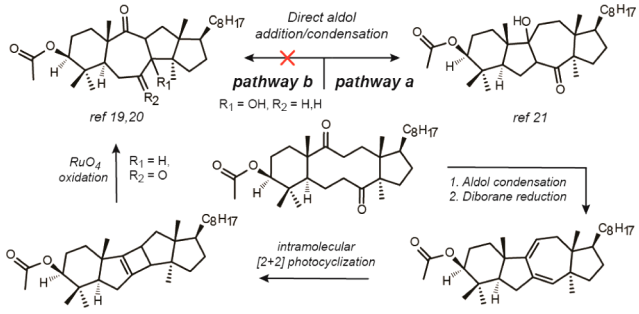


Figure 1. Divergent aldol reaction of lanosterol-derived diketone.

The starting material **1** was prepared from a commercially available mixture of lanosterol (60%) and 24,25-dihydrolanosterol (40%) according to the method developed by Reshetova et al.[24] and recently validated in our laboratory.[4] In order to gain access to the desired diketone **2**, the starting material **1** was oxidized with ruthenium tetroxide under Sharpless conditions.[25] Under these conditions, the bridging double bond at the B/C ring fusion underwent competing oxidative cleavage reaction to give diketone **2** and nonselective allylic oxidation at C-11 and C-7 to give α,β-unsaturated ketones **3** and **4**, respectively (Scheme 1).

With the diketone **2** in hand, we directed our efforts toward the identification of conformational preferences of this

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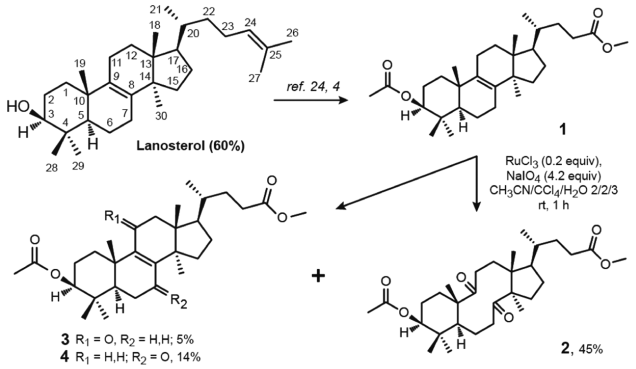
Scheme 1. Synthesis of Diketone 2 from Commercial Mixture of Lanosterol (60%) and Dihydrolanosterol (40%)



molecule. Molecular modeling revealed the potentiality of existence of two conformations of the cyclodecane ring of diketone **2**. In particular, we proposed a "boat (with bow at C-5 and stern between C-8 and C-11)−chair−boat (with bow between C-9 and C-7 and stern at C-14)" (BCB) conformer and "chair −chair −chair" (CCC) conformer. Energy minimization calculations[26] at the B3LYP 6-311G(d,p) level of theory disclosed that the conformer CCC is thermodynamically more stable than the canonical conformer BCB by 4.3 kcal/mol. Additionally, a set of resonances corresponding to only one conformational isomer was observed in the ^{1}H and ^{13}C NMR spectra of diketone **2**. We would argue that these facts strongly suggest that diketone **2** exists in the solution as a single conformational isomer CCC (Figure 2).

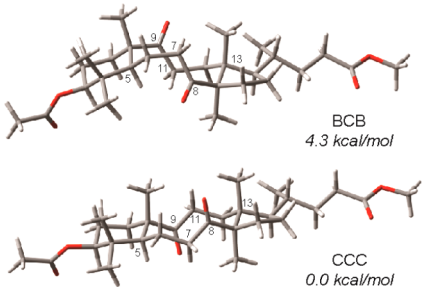


Figure 2. Conformational analysis of diketone **2**.

Further analysis of the substrate-dictated conformer CCC revealed that the pseudoaxial H-7 is antiperiplanar with the carbonyl at C-8, and the pseudoequatorial H-7 is orthogonal to the C═O bond. Thus, the *Z*-enolate should be formed as a key intermediate after deprotonation of **2** by the loss of the pseudoequatorial α-hydrogen. We have envisioned that under common aldol conditions, such as Brønsted acid catalysis, this enolate would be structurally biased to form product **5** with *syn* configuration at the newly formed B/C ring fusion (Figure 3).

The power of Lewis acid catalysis to govern the diastereoselectivity of aldol addition is well-known.[27,28] With this in mind, we hypothesized that when treated with a Lewis acid, such as neutral alumina, the key intermediate may engage in a six-membered Zimmerman−Traxler transition state.[29] This transition state would determine the β-facial position of H-7, as well as α-facial position of the keto groups at C-8 and C-9, thus providing product **6** with a *trans* configuration at the B/C ring fusion. It is noteworthy that Fox and Scott[21] have assumed that products **5** and **6** would be epimeric with respect to the β-hydroxy group at C-9. In contrast, our stereochemical model suggested that the difference between these epimeric products lies in the absolute stereochemistry of α-hydrogen at C-7.

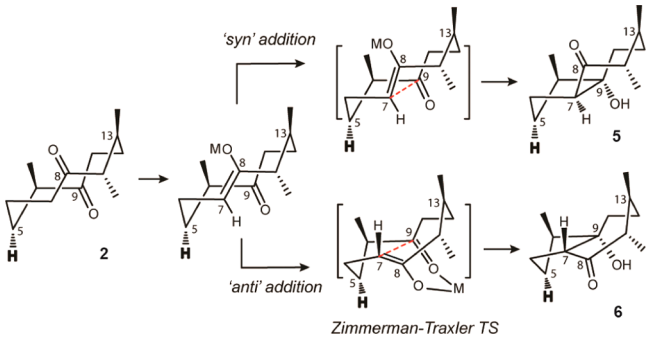
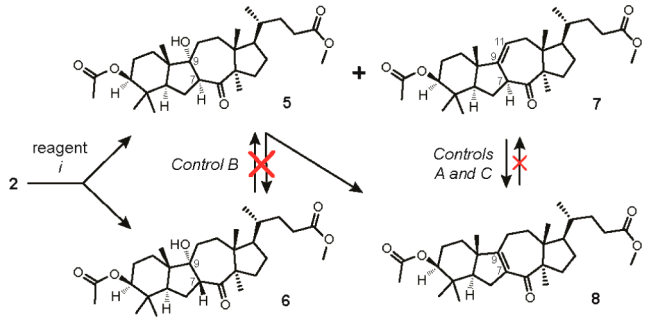


Figure 3. Working model demonstrates the role of the enolate geometry and the conformation of cyclodecane ring of diketone **2** toward stereoselectivity.

In complete agreement with this rationale, predominant formation of product **5** was observed when diketone **2** was subjected to the standard aldol conditions. Specifically, the use of pyrrolidine as an organocatalyst for enamine-mediated aldol reaction led to the formation of product **5** in 86% yield after 48 h and no other products were observed (Table 1, entry 1).

Table 1. Aldol Addition Reaction of Diketone 2 under Common Aldol Conditions[a]



		isolated yield of product (%)			
entry	reagent *i*	**5**	**6**	**7**	**8**
1	pyrrolidine (0.5 equiv)	86	0	0	0
2	TFA (0.2 equiv)	72[b]	0	0	7[b]
3	TFA (0.5 equiv)	71[c]	0	10[c]	4[c]
4	TFA (5 equiv)	0	0	48	32
5	Al_2O_3 neutral (100 equiv)	35	23	0	11
6	Al_2O_3 basic (100 equiv)	11	30	0	9
7	LDA (1.1 equiv)	40	6	0	6
8	$TiCl_4$ (1.2 equiv)	0	0	0	58

[a]Control A: TFA (5 equiv), 48 h (**8**, 90% yield). Control B: Al_2O_3 neutral (100 equiv), 48 h (**8**, 17% yield; **5**, 78% recovery). Control C: Al_2O_3 neutral (100 equiv), 45 min (**8**, 95% yield). [b]brsm, 65% conversion. [c]brsm, 91% conversion.

In due course, treatment of diketone **2** with 0.2 equiv of TFA in DCM for 48 h yielded *syn*-adduct **5** and α,β-unsaturated ketone **8** in 72% and 7% yield, respectively (Table 1, entry 2). The formation of ketone **8** in this reaction suggested the possible intermediacy of *anti*-adduct **6**, which has an antiperiplanar arrangement of H-7 and the hydroxyl group at C-9, thus raising the possibility of the increased production of ketone **8** if overall elimination of water is to occur through E2-

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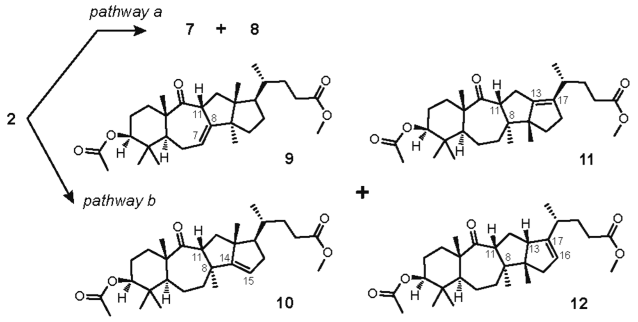
Table 2. Aldol Reaction of Diketone 2 via Pathway b



				isolated yield of product[b] (%)					
entry	reagent[a]	temp (°C)	time (h)	7	8	9	10	11	12
1	$BF_3{\cdot}Et_2O$[c]	−78 to rt	48	10	39	7	2	7	15
2	$Al(OTf)_3$	rt	96	30[d]	14[d]	11[d]	11[d]	5[d]	0
3	$Sc(OTf)_3$	rt	48	9[e]	0	7[e]	5[e]	6[e]	0
4	$In(OTf)_3$	rt	48	17	17	8	11	7	2
5	$Sc(OTf)_3$	50	72	11[f]	16[f]	11[f]	9[f]	14[f]	6[f]
6	$In(OTf)_3$	50	7	9	21	7	12	6	3
7	$InCl_3$	50	54	3	33	1	0	10	21
8	$Cu(OTf)_2$	50	16	0	42	0	10	9	17

[a]Unless otherwise indicated, all reactions were performed in 0.1 M solutions of DCM with 0.2 equiv of the catalyst. [b]Yields of 7 and **9**−**12** were determined by ^{1}H NMR. [c]Reaction performed with 1.1 equiv of the reagent (−78 °C to rt). [d]brsm, 74% conversion. [e]brsm, 55% conversion. [f]brsm, 90% conversion.

type transition state. When 0.5 equiv of TFA was used in this reaction, products **5** and **8** were accompanied by the formation of ketone **7** (10%, Table 1, entry 3). Furthermore, the use of excess TFA led to the predominant formation of ketone **7**, and no products of aldol addition were detected in the reaction mixture (Table 1, entry 4). α-Facial position of H-7 in ketone **7** allowed us to suggest that under the acidic reaction conditions diketone **2** was initially converted to *syn*-adduct **5**, followed by the E1-type elimination reaction to form ketones **7** and **8**.[5] Ketone **7**, in turn, underwent simultaneous double bond migration process leading to the increased production of α,β-unsaturated ketone **8**. The control experiment confirmed our suggestion when isolated ketone **7** was treated with excess TFA to form α,β-unsaturated ketone **8** in 90% yield after 48 h (Table 1, control A)

Concurrently, treatment of diketone **2** with neutral alumina led to the formation of *anti*-adduct **6**, *syn*-adduct **5**, and α,β-unsaturated ketone **8** in 23%, 35%, and 11% yield, respectively (Table 1, entry 5). The use of basic alumina in this reaction resulted in the increased formation of *anti*-adduct **6**, although considerable degradation was observed (Table 1, entry 6). Given the fact that aldol addition is generally known to be a reversible process, we set out to determine whether the distribution of products **5** and **6** was the result of thermodynamic reaction control. Thus, when purified *syn*-adduct **5** was resubjected to the same reaction conditions, no direct interconversion of **5** and **6** was indicated. However, the formation of α,β-unsaturated ketone **8** in 17% yield was noted (Table 1, control B). One possible explanation for the formation of **8** in the control experiment is the equilibration between *syn*-adduct **5** and *anti*-adduct **6**, followed by simultaneous dehydration of **6**. Alternatively, intermediate formation of ketone **7** by dehydration of starting material **5** could be suggested. When pure ketone **7** was resubjected to the conditions of the same control experiment, α,β-unsaturated ketone **8** was formed in 98% yield after 45 min (Table 1, control C). We would argue that the absence of direct interconversion of **5** and **6**, coupled with the rapid formation of **8** from **7**, strongly suggest that the formation of *anti*-adduct **6** is the result of Lewis acid controlled transition state of the aldol addition reaction of diketone **2**.

Encouraged by the success of these early studies, we set out to achieve complete control over the diastereoselectivity of this transannular reaction by screening a range of Lewis acids of varying strength and atomic radius of the metal cation. The lithium cation is generally known to reliably follow the Zimmerman−Traxler model.[26] Hence, upon reaction with LDA (1.1 equiv, −78 °C to rt), diketone **2** yielded *syn*-adduct **5**, *anti*-adduct **6**, and α,β-unsaturated ketone **8** in 40%, 6%, and 6% yield, respectively (Table 1, entry 7). The use of $TiCl_4$ in the presence of the tertiary amine (1.1 equiv, −78 °C to rt) led to the formation of α,β-unsaturated ketone **8** in 58% yield, and no other products were observed (Table 1, entry 8).

In due course, treatment of diketone **2** with $BF_3{\cdot}Et_2O$ (1.1 equiv, −78 °C to rt) unexpectedly resulted in the formation of aliphatic ketones **9**−**12** via pathway b, accompanied by the products of pathway a **7** and **8** (Table 2, entry 1).

Similar product distribution was observed when 0.2 equiv of $Al(OTf)_3$, $Sc(OTf)_3$, and $In(OTf)_3$ was used to catalyze the aldol addition of **2** at rt (Table 2, entries 2−4). The use of $InCl_3$ and $Cu(OTf)_2$ at rt led to the full recovery of the starting material. Increasing the temperature to 50 °C significantly improved the efficiency of this transformation (Table 2, entries 5−8). Thus, $InCl_3$ proved to be the reagent of choice for the highest yield of **12**. Alternative catalysts such as $Zn(OTf)_2$, $Yb(OTf)_3$, and $La(OTf)_3$ did not show any reactivity after 24 h under both of the optimized reaction conditions. The fact that the formation of the desired *anti*-adduct **6** was not observed under our Lewis acidic conditions was disappointing. However, the unexpected formation of steroid analogues **9**−**12** with 6/7/5/5 ring composition is important because it constitutes the discovery of a formerly intractable pathway of a well-known

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reaction and, therefore, provides direct access to the area of chemical space which has not yet been explored.

The absolute stereochemistry of H-11 in **9**–**12** suggested the following mechanistic rationale for the formation of these molecules. Presumably, the *Z*-enolate of diketone **2** can be formed upon deprotonation by the loss of pseudoequatorial *α*-hydrogen at C-11. This enolate is geometrically predisposed for the formation of intermediate aldol adduct via pathway b with *syn* configuration at the B/C ring fusion. Upon further in situ reaction with a strong Lewis acid, such as $BF_3{\cdot}Et_2O$, the *syn*-adduct engages in E1-type transition state to form a carbocationic intermediate, which, in turn, may be followed by either elimination of H-7 to give **9** or C-30 methide shift and elimination of H-15 to give **10**. Additionally, the carbocation can be followed by a cascade of C-30 and C-18 methide shifts and an elimination of H-17 to form **11** (Figure 4).

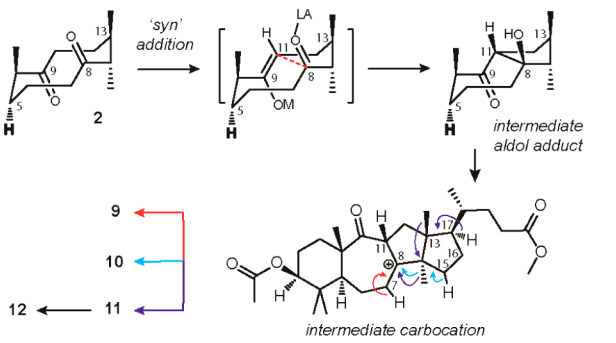

Figure 4. Mechanistic rationale for the formation of **9**–**12** via pathway b.

The formation of ketone **12** deserves a separate comment. Analogously with ketones **10** and **11**, the formation of Δ16,17 double bond in **12** may result from sequential C-30 and C-18 methide shifts, H-17 hydride shift, and an elimination of H-16. However, *α*-facial position of H-17 in the intermediate carbocation and the resultant *β*-facial orientation of H-13 in ketone **12** led to a conclusion that the Δ16,17 double bond in **12** is the result of allylic shift and migration of *β*-oriented pseudoaxial H-16 of ketone **11**.

In conclusion, we have devised and executed a DOS strategy whereby lanosterol-derived diketone **2** was used as a substrate for nonregioselective aldol reaction leading to 6/5/7/5- and 6/7/5/5-fused triterpenoid analogues. We hope that the observed formation of 6/7/5/5-fused products will allow for the consideration of transannular aldol reaction as a linchpin step for the construction of bicyclo[3.3.0]octane fragment in the total syntheses of complex molecules that contain such moiety within their ring systems.[30,31]

EXPERIMENTAL SECTION

(*R*)-Methyl 4-((3*S*,5*R*,10*S*,13*R*,14*R*,17*R*)-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 (1). Starting material **1** was prepared from the commercially available mixture of lanosterol (60%) and 24,25-dihydrolanosterol (40%) in three steps by a previously published method[24,4] (white solid, 3.9 g, 65%). The identity of **1** was confirmed by ^{1}H and ^{13}C NMR spectra. The purity of **1** was determined by ^{1}H NMR, TLC, and mp. Physical and spectroscopic data were found to match literature[4] data.

Preparation of 2–4. In a 200 mL single-neck round-bottom flask, $RuCl_3$ (87 mg, 0.42 mmol) was added in one portion to a solution of $NaIO_4$ (1.89 g, 8.82 mmol) in 63 mL of H_2O, and the resulting suspension was stirred open to atmosphere for 15 min, followed by the addition of 42 mL of acetonitrile. The solution of starting material **1** (1 g, 2.1 mmol) in 42 mL of CCl_4 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 1 h, at which time 5 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 Na_2SO_4 and concentrated under vacuum, and the crude mixture of products was further separated by careful column chromatography on silica to yield *α*,*β*-unsaturated ketone **3** as a white solid (48 mg, 5%): R_f = 0.31 (EA/hex = 25/75), *α*,*β*-unsaturated ketone **4** as a white solid (140 mg, 14%), R_f = 0.28 (EA/hex =25/75), and diketone **2** as a white solid (480 mg, 45%), R_f = 0.25 (EA/hex =25/75).

(R)-Methyl 4-((1R,3aR,6aS,8S,10aS,13aR)-8-Acetoxy-3a,7,7,10a,13a-pentamethyl-4,11-dioxohexadecahydro-1H-benzo-[a]cyclopenta[f][10]annulen-1-yl)pentanoate (2). White solid. Mp: 180–183 °C (lit.[32] mp 175–177 °C). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 4.54 (dd, J_1 = 11.6 Hz, J_2 = 4.4 Hz, 1H), 3.64 (s, 3H), 2.02 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 217.1, 215.8, 174.5, 170.7, 79.8, 61.7, 54.6, 51.9, 51.6, 51.5, 50.9, 40.8, 39.5, 37.3, 35.0, 32.8, 31.51, 31.48, 31.1, 28.0, 25.8, 24.6, 23.3, 21.3, 20.6, 19.8, 19.3, 16.8, 16.7, 15.8. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{48}O_6Na^+$ $[M + Na]^+$ 527.33431, found 527.33436.

(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-tetradeca-hydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (3). The identity of **3** was confirmed by ^{1}H and ^{13}C NMR spectra. The purity of **3** was determined by ^{1}H NMR, TLC, and mp. Physical and spectroscopic data were found to match literature[4] data.

(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-tetradeca-hydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (4). The identity of **4** was confirmed by ^{1}H and ^{13}C NMR spectra. the purity of **4** was determined by ^{1}H NMR, TLC, and mp. Physical and spectroscopic data were found to match literature[4] data.

Preparation of 5–8. *Table 1 (Entry 1).* Pyrrolidine (7 mg, 0.099 mmol, 8.1 *μ*L) was added dropwise to the solution of diketone **2** (100 mg, 0.198 mmol) in DCM (2 mL). The flask was then sealed with a glass stopper, and the resulting solution was stirred vigorously at rt for 48 h, at which time water was added to the reaction mixture. Layers were separated, and the aqueous layer was extracted with DCM. The organic layer was washed with brine and subsequently dried over Na_2SO_4. The solvent was removed in vacuo, and the crude product was purified by column chromatography on silica to give **5** as a white solid (86 mg, 86%).

General Procedure A for the Reaction of 2 with TFA. A specified amount of TFA was added dropwise to the solution of the diketone **2** (1 equiv) in DCM (0.05 M in starting material). A flask was then sealed with a glass stopper, and the resulting solution was stirred vigorously at rt for a specified amount of time, until the starting material was consumed or decomposition was observed, as determined by TLC. After removal of the solvent in vacuo, products **5**, **7**, **8**, and unreacted diketone **2** were isolated by column chromatography on silica with the mixture of ethyl acetate and hexanes (20/80) as eluting solvent.

Table 1 (Entry 2). Following the general procedure A for the reaction of **2** with TFA, the use of diketone **2** (100 mg, 0.198 mmol), TFA (4.5 mg, 0.0396 mmol, 3 *μ*L), and DCM (4 mL) yielded **8** (4.2 mg, 7% brsm), unreacted **2** (35.4 mg, 65% conversion), and **5** (47.1 mg, 72% brsm).

Table 1 (Entry 3). Following the general procedure A for the reaction of **2** with TFA, the use of diketone **2** (100 mg, 0.198 mmol), TFA (11.4 mg, 0.0991 mmol, 7.6 *μ*L), and DCM (4 mL) yielded **7** (8.4 mg, 10% brsm), **8** (3.4 mg, 4% brsm), unreacted **2** (9.3 mg, 91% conversion), and **5** (64.7 mg, 71% brsm).

Table 1 (Entry 4). Following the general procedure A for the reaction of **2** with TFA, the use of diketone **2** (100 mg, 0.198 mmol),

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TFA (112.9 mg, 0.99 mmol, 76 μL), and DCM (4 mL) yielded **7** (46.1 mg, 48% brsm) and **8** (31.2 mg, 32% brsm).

Table 1 (Entry 5). A round-bottom flask open to atmosphere was charged with neutral alumina (2 g, 19.8 mmol), followed by the addition of DCM (1 mL). A solution of **2** (100 mg, 0.198 mmol) in DCM (1 mL) was then added to the resulting suspension. The flask was sealed with a glass stopper, and the reaction mixture was vigorously stirred at rt for 48 h, at which time the mixture was filtered over a fine sintered funnel and washed successively with ethyl acetate. After the removal of the solvent in vacuo, careful column chromatography on silica yielded **8** as a white solid (10.8 mg, 11%): R_f = 0.32 (EA/hex = 25/75), **6** as a white solid (22.9 mg, 23%), R_f = 0.15 (EA/hex = 25/75), and **5** as a white solid (35.3 mg, 35%), R_f = 0.14 (EA/hex = 25/75).

Table 1 (Entry 6). A round-bottom flask open to atmosphere was charged with basic alumina (2 g, 19.8 mmol), followed by the addition of DCM (1 mL). A solution of **2** (100 mg, 0.198 mmol) in DCM (1 mL) was then added to the resulting suspension. The flask was sealed with a glass stopper, and the reaction mixture was vigorously stirred at rt for 48 h, at which time the mixture was filtered over a fine sinter funnel and washed successively with ethyl acetate. After the removal of the solvent in vacuo, careful column chromatography on silica yielded **8** as a white solid (8.5 mg, 9%): R_f = 0.32 (EA/hex =25/75), **6** as a white solid (29.8 mg, 30%), R_f = 0.15 (EA/hex = 25/75), and **5** as a white solid (10.7 mg, 11%), R_f = 0.14 (EA/hex = 25/75).

Table 1 (Entry 7). The solution of diisopropylamine (11 mg, 0.109 mmol, 15 μL) in dry THF (3 mL) in a flame-dried (under vacuum) round-bottom flask was cooled to −78 °C, followed by a dropwise addition of *n*-butyllithium (2.5 M in hexanes, 43.6 μL). The reaction mixture was warmed to 0 °C, stirred at this temperature for 5 min, and subsequently cooled to −78 °C. A solution of **2** (50 mg, 0.0991 mmol) in dry THF (2 mL) was then added dropwise to the solution of LDA by a syringe at −78 °C. The cooling bath was then removed, and the reaction mixture was allowed to warm to rt and stirred at rt a the total of 15 h. After solvent removal in vacuo, the residue was taken up in DCM and washed with water and brine. The organic layer was dried over Na_2SO_4. Evaporation of the solvent in vacuo gave crude product mixtures that were further separated by careful column chromatography on silica to give **8** as a white solid (3.1 mg, 6%): R_f = 0.32 (EA/hex = 25/75), **6** as a white solid (3.2 mg, 6%), R_f = 0.15 (EA/hex = 25/75), and **5** as a white solid (19.8 mg, 40%), R_f = 0.14 (EA/hex = 25/75).

Table 1 (Entry 8). Dry DCM (0.5 mL) was added to a flame-dried (under vacuum) round-bottomed flask. The flask was cooled to −78 °C, and $TiCl_4$ (22.6 mg, 0.1189 mmol, 13 μL) was added at that temperature by a quick syringe transfer, followed by a dropwise addition of diisopropylethylamine (17.9 mg, 0.139 mmol, 24 μL). A solution of diketone **2** (50 mg, 0.0991 mmol) in dry DCM (0.5 mL) was added to the reaction mixture at −78 °C, and the reaction mixture was allowed to warm to rt and stirred at rt overnight, at which time water (1 mL) was added to the solution, layers were separated, and the aqueous layer was extracted with DCM. The organic layer was dried with Na_2SO_4, concentrated under vacuum and the crude product was purified by column chromatography on silica to give **8** (28 mg, 58%) as a white solid.

*(R)-Methyl 4-((1R,3aR,4aS,5aS,7S,9aS,9bR,11aR)-7-Acetoxy-9b-hydroxy-3a,6,6,9a,11a-pentamethyl-4-oxohexadecahydro-1H-benzo[a]cyclopenta[f]azulen-1-yl)pentanoate (**5**).* White solid. Mp: 206−208 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.53 (m, 1H), 3.65 (s, 3H), 3.34 (dd, $J_1 = J_2$ = 9 Hz, 1H), 2.04 (s, 3H), 1.35 (s, 3H), 0.99 (s, 3H), 0.92 (d, J = 6 Hz, 3H), 0.91 (s, 3H), 0.76 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): δ CH_3: 51.7, 29.64, 21.9, 21.4, 19.3, 17.6, 16.8, 16.2; CH_2: (2 × 31.4), 30.6, 29.56, 29.4, 28.5, 27.2, 24.6, 23.2; CH_1: 81.1, 57.6, 51.3, 49.1, 35.4; CH_0: 212.2, 174.6, 171.2, 81.9, 63.4, 48.7, 46.7, 37.1. HRMS (ESI): m/z calcd for $C_{30}H_{48}O_6Na^+$ $[M + Na]^+$ 527.3348, found 527.3340.

*(R)-Methyl 4-((1R,3aR,4aR,5aS,7S,9aS,9bR,11aR)-7-Acetoxy-9b-hydroxy-3a,6,6,9a,11a-pentamethyl-4-oxohexadecahydro-1H-benzo[a]cyclopenta[f]azulen-1-yl)pentanoate(**6**).* White solid. Mp: 172−174 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.49 (dd, J_1 = 11.4 Hz, J_2 = 4.2 Hz, 1H), 3.67 (s, 3H), 3.23 (dd, J_1 = 11.4 Hz, J_2 = 5.4 Hz, 1H), 2.05 (s, 3H), 1.30 (s, 3H), 0.99−0.98 (9H), 0.95 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): δ CH_3: 51.7, 29.03, 22.9, 21.3, 20.0, 17.2, 16.45, 16.40; CH_2: 34.2, 31.6, 31.1, 29.7, 28.95, 28.0, 24.8, 24.6, 21.7; CH_1: 81.3, 58.6, 51.4, 48.2, 35.1; CH_0: 215.7, 174.6, 171.2, 83.5, 63.0, 50.0, 45.5, 37.3. HRMS (ESI): m/z calcd for $C_{30}H_{48}O_6Na^+$ $[M + Na]^+$ 527.33431, found 527.33453.

*(R)-Methyl 4-((1R,3aR,4aS,5aR,7S,9aS,11aR)-7-Acetoxy-3a,6,6,9a,11a-pentamethyl-4-oxo-2,3,3a,4,4a,5,5a,-6,7,8,9,9a,11,11a-tetradecahydro-1H-benzo[a]cyclopenta[f]azulen-1-yl)pentanoate (**7**).* White foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25 (ddd, J_1 = 9.2 Hz, J_2.= J_3 =3.5 Hz, 1H), 4.52 (dd, J_1 = 11.5 Hz, J_2.= 4.8 Hz, 1H), 3.94 (m, 1H), 3.66 (s, 3H), 2.05 (s, 3H), 1.30 (d, J = 0.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): δ CH_3: 51.7, 28.9, 23.0, (2 × 21.4), 19.7, 16.9, 16.3; CH_2: 34.92, 32.0, 31.6, 31.1, 30.1, 25.6, 25.3, 22.5; CH_1: 116.0, 81.2, 54.0, 50.9, 50.6, 34.98; CH_0: 210.1, 174.6, 171.2, 150.3, 62.9, 49.4, 45.4, 37.5. HRMS (ESI): m/z calcd for $C_{30}H_{46}O_5Na^+$ $[M + Na]^+$ 509.32375, found 509.32376.

*(R)-Methyl 4-((1R,3aR,5aR,7S,9aS,11aR)-7-Acetoxy-3a,6,6,9a,11a-pentamethyl-4-oxo-2,3,3a,4,5,5a,6,7,-8,9,9a,10,11,11a-tetradecahydro-1H-benzo[a]cyclopenta[f]azulen-1-yl)pentanoate (**8**).* White solid. Mp: 154−156 °C (lit.[32] mp 155−158 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (dd, J_1 = 11.2 Hz, J_2 = 4.8 Hz, 1H), 3.66 (s, 3H), 2.05 (s, 3H), 1.11 (s, 3H), 1.00 (s, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): δ CH_3: 51.7, 28.7, 24.1, 21.4, 20.1, 17.1, 17.0, 15.0; CH_2: 33.7, 31.7, 31.2, 30.9, 30.4, 30.3, 25.2, 24.4, 22.8; CH_1: 80.9, 54.9, 51.6, 34.6; CH_0: 206.1, 174.6, 171.2, 160.7, 135.8, 62.7, 50.4, 45.2, 37.3. HRMS (ESI): m/z calcd for $C_{30}H_{46}O_5Na^+$ $[M + Na]^+$ 509.32375, found 509.32372.

Control Experiment A. TFA (23.4 mg, 0.206 mmol, 16 μL) was added dropwise to the solution of the ketone **7** (20 mg, 0.041 mmol) in DCM (0.8 mL). The flask was then sealed with a glass stopper and the resulting solution was stirred vigorously at rt for 48 h. After removal of the solvent in vacuo, column chromatography of the crude mixture on silica yielded **8** as a white solid (18.1 mg, 90%), R_f = 0.32 (EA/hex =25/75).

Control experiment B. A round-bottom flask open to atmosphere was charged with neutral alumina (404 mg, 4 mmol), followed by the addition of DCM (0.2 mL). A solution of **5** (20 mg, 0.04 mmol) in DCM (0.2 mL) was then added to the resulting suspension. The flask was sealed with a glass stopper and the reaction mixture was vigorously stirred at rt for 48 h, at which time the mixture was filtered over a fine sinter funnel and washed successively with ethyl acetate. After the removal of the solvent in vacuo, careful column chromatography on silica yielded **8** as a white solid (3.5 mg, 17%), R_f = 0.32 (EA/hex =25/75); and unreacted **5** as a white solid (15.6 mg, 78% recovery), R_f = 0.14 (EA/hex =25/75).

Control experiment C. A round-bottom flask open to atmosphere was charged with neutral alumina (419 mg, 4.11 mmol), followed by the addition of DCM (0.2 mL). A solution of **7** (20 mg, 0.041 mmol) in DCM (0.2 mL) was then added to the resulting suspension. The flask was sealed with a glass stopper and the reaction mixture was vigorously stirred at rt for 45 min, at which time the mixture was filtered over a fine sinter funnel and washed successively with ethyl acetate. After the removal of the solvent in vacuo, careful column chromatography on silica yielded **8** as a white solid (19 mg, 95%), R_f = 0.32 (EA/hex =25/75).

Preparation of 7−12. *Table 2 (Entry 1).* A solution of diketone **2** (100 mg, 0.198 mmol) in dry DCM (1 mL) in a flame-dried (under vacuum) round-bottom flask was cooled to −78 °C, followed by a dropwise addition of $BF_3{\cdot}Et_2O$ (purified, redistilled) (30.9 mg, 0.218 mmol, 27 μL) at this temperature. The reaction mixture was allowed to warm up to rt overnight and stirred at this temperature for the total of 48 h, at which time the solvent was removed under vacuum, water (2 mL) was added to the solution, layers were separated, and the aqueous layer was extracted with DCM. The organic layer was dried with Na_2SO_4 and concentrated under vacuum, and the crude mixture of products was separated by column chromatography on silica to give

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an inseparable mixture (43 mg), containing **7** (9.9 mg, 10%), **9** (6.4 mg, 7%), **10** (2 mg, 2%), **11** (6.9 mg, 7%), and **12** (14.3 mg, 15%) as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), and pure α,β-unsaturated ketone **8** (38 mg, 39%), R_f = 0.25 (EA/hex = 20/80).

General procedure B for Reaction of 2 with Lewis acid Catalysts at rt. A specified Lewis acid catalyst (0.2 equiv) was added in one portion to the solution of diketone **2** (1 equiv) in DCM (0.1 M in diketone) in a flame-dried round-bottom flask at rt. The flask was sealed with a glass stopper, and the resulting solution was stirred vigorously at rt for a specified amount of time, until the starting material was consumed or decomposition was observed, as determined by TLC. After the solvent was removed in vacuo, the crude mixture of products was separated by column chromatography on silica with the specified ethyl acetate−hexanes mixtures.

Table 2 (Entry 2). Following the general procedure B for the reaction of **2** with Lewis acid catalysts, the use of diketone **2** (50 mg, 0.0991 mmol), aluminum triflate (9.4 mg, 0.0198 mmol) and DCM (1 mL) for 96 h yielded an inseparable mixture (20.2 mg), containing **7** (10.7 mg, 30% brsm), **9** (3.9 mg, 11% brsm), **10** (3.9 mg, 11% brsm) and **11** (1.8 mg, 5% brsm), as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), pure α,β-unsaturated ketone **8** (5.1 mg, 14% brsm), R_f = 0.25 (EA/hex = 20/80), and unreacted diketone **2** (12.8 mg, 74% conversion), R_f = 0.17 (EA/hex = 20/80).

Table 2 (Entry 3). Following the general procedure B for the reaction of **2** with Lewis acid catalysts, the use of diketone **2** (50 mg, 0.0991 mmol), scandium triflate (10 mg, 0.01982 mmol) and DCM (1 mL) for 48 h yielded an inseparable mixture (7.7 mg), containing **7** (2.3 mg, 9% brsm), **9** (1.8 mg, 7% brsm), **10** (1.3 mg, 5% brsm), and **11** (1.7 mg, 6% brsm), as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), and pure unreacted diketone **2** (22.3 mg, 55% conversion), R_f = 0.17 (EA/hex = 20/80).

Table 2 (Entry 4). Following the general procedure B for the reaction of **2** with Lewis acid catalysts, the use of diketone **2** (50 mg, 0.0991 mmol), indium triflate (11 mg, 0.0198 mmol), and DCM (1 mL) for 48 h yielded an inseparable mixture (22.3 mg), containing **7** (8.1 mg, 17%), **9** (3.9 mg, 8%), **10** (5.3 mg, 11%), **11** (3.1 mg, 7%), and **12** (0.8 mg, 2%), as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), and pure α,β-unsaturated ketone **8** (8 mg, 17%), R_f = 0.25 (EA/hex = 20/80).

General Procedure C for Reaction of 2 with Lewis acid Catalysts at 50 °C. A specified Lewis acid catalyst (0.2 equiv) was added in one portion to the solution of diketone **2** (1 equiv) in DCM (0.1 M in diketone) in a 5 mL Schlenk tube at rt. The tube was filled with argon and subsequently sealed with a Teflon stopper. The resulting solution was stirred vigorously at 50 °C for a specified amount of time, until the starting material was consumed or decomposition was observed, as determined by TLC. The solvent was removed in vacuo, and the crude mixture of products was separated by column chromatography on silica with the specified ethyl acetate−hexanes mixtures.

Table 2 (Entry 5). Following the general procedure C for the reaction of **2** with Lewis acid catalysts, the use of diketone **2** (50 mg, 0.0991 mmol), scandium triflate (10 mg, 0.01982 mmol), and DCM (1 mL) for 72 h yielded an inseparable mixture (24.1 mg), containing **7** (4.7 mg, 11% brsm), **9** (4.9 mg, 11% brsm), **10** (4.1 mg, 9% brsm), **11** (6.1 mg, 14% brsm), and **12** (2.6 mg, 6% brsm), as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), pure α,β-unsaturated ketone **8** (7 mg, 16% brsm), R_f = 0.25 (EA/hex = 20/80), and unreacted diketone **2** (5 mg, 90% conversion), R_f = 0.17 (EA/hex = 20/80).

Table 2 (Entry 6). Following the general procedure C for the reaction of **2** with Lewis acid catalysts, the use of diketone **2** (50 mg, 0.0991 mmol), indium triflate (11 mg, 0.01982 mmol), and DCM (1 mL) for 7 h yielded an inseparable mixture (20 mg), containing **7** (4.2 mg, 9%), **9** (3.5 mg, 7%), **10** (5.6 mg, 12%), **11** (3.1 mg, 6%), and **12** (1.6 mg, 3%), as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), and pure α,β-unsaturated ketone **8** (7 mg, 21%), R_f = 0.25 (EA/hex = 20/80).

Table 2 (Entry 7). Following the general procedure C for the reaction of **2** with Lewis acid catalysts, the use of diketone **2** (50 mg, 0.0991 mmol), indium(III) chloride (4.4 mg, 0.01982 mmol) and DCM (1 mL) for 54 h yielded an inseparable mixture (19.5 mg), containing **7** (1.6 mg, 3%), **9** (0.6 mg, 1%), **11** (4.6 mg, 10%), and **12** (10 mg, 21%), as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), and pure α,β-unsaturated ketone **8** (15.8 mg, 33%), R_f = 0.25 (EA/hex = 20/80).

Table 2 (Entry 8). Following the general procedure C for the reaction of **2** with Lewis acid catalysts, the use of diketone **2** (50 mg, 0.0991 mmol), copper(II) triflate (7.2 mg, 0.01982 mmol), and DCM (1 mL) for 16 h yielded an inseparable mixture (20 mg), containing **10** (4.6 mg, 10%), **11** (4.4 mg, 9%), and **12** (8 mg, 17%), as determined by ^{1}H NMR, R_f = 0.32 (EA/hex = 20/80), and pure α,β-unsaturated ketone **8** (20 mg, 42%), R_f = 0.25 (EA/hex = 20/80).

*(R)-Methyl 4-((1R,3aR,5aS,7S,9aS,10aR,11aR)-7-Acetoxy-3a,6,6,9a,11a-pentamethyl-10-oxo-2,3,3a,5,5a,6,7,8,-9,9a,10,10a,11,11a-tetradecahydro-1H-benzo[f]cyclopenta[a]-azulen-1-yl)pentanoate (**9**).* Transparent oil. ^{1}H NMR (600 MHz, C_6D_6): δ 5.37 (m, 1H), 4.60 (dd, J_1 = 12 Hz, J_2 = 4.6 Hz, 1H), 4.29 (ddd, J_1 = J_2 = 8 Hz, J_1 = 1.6 Hz, 1H), 3.40 (s, 3H), 2.64 (dd, J_1 = 12 Hz, J_2 = 9 Hz, 1H), 1.71 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.76 (d, J = 6.4 Hz, 3H), 0.71 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6, DEPT): δ CH_3: 51.0, 28.1, 24.8, 20.8, 19.8, 18.0, 17.8, 16.7; CH_2: 33.9, 33.4, 32.6, 31.5, 30.9, 28.5, 24.0, 23.7; CH_1: 120.1, 79.4, 55.15, 55.14, 35.3, 46.0; CH_0: 206.7, 173.8, 169.6, 148.5, 61.9, 54.3, 52.3, 40.1. HRMS (ESI): m/z calcd for $C_{30}H_{46}O_5Na^+$ $[M + Na]^+$ 509.32375, found 509.32394.

*(R)-Methyl 4-((1R,3bS,5aS,7S,9aS,10aR,11aR)-7-Acetoxy-3b,6,6,9a,11a-pentamethyl-10-oxo-2,3b,4,5,5a,6,7,8,9,-9a,10,10a,11,11a-tetradecahydro-1H-benzo[f]cyclopenta[a]-azulen-1-yl)pentanoate (**10**).* White foam. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.13 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 1H), 4.46 (m, 1H), 3.79 (dd, J_1 = 12 Hz, J_2 = 4.9 Hz, 1H), 3.66 (s, 3H), 2.05 (s, 3H), 1.16 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.84 (d, J = 6.8 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): δ CH_3: 51.7, 31.0, 28.0, 21.4, 18.6, 18.0, 17.1, 16.4; CH_2: 39.7, 39.5, 38.9, 31.8, 31.4, 30.3, 23.6, 23.5; CH_1: 115.7, 80.3, 60.1, 56.6, 45.4, 32.8; CH_0: 212.6, 174.8, 170.9, 170.3, 54.6, 49.4, 40.4, 40.3. HRMS (ESI): m/z calcd for $C_{30}H_{46}O_5Na^+$ $[M + Na]^+$ 509.32375, found 509.32392.

*(R)-Methyl 4-((3aR,3bS,5aS,7S,9aS,10aR)-7-Acetoxy-3a,3b,6,6,9a-pentamethyl-10-oxo-3,3a,3b,4,5,5a,6,7,8,9,9a,10,10a,11-tetradeca-hydro-2H-benzo[f]cyclopenta[a]azulen-1-yl)pentanoate (**11**).* Transparent oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.47 (dd, J_1 = 11.8 Hz, J_2 = 3.9 Hz, 1H), 3.84 (dd, J_1 = J_2 = 9 Hz, 1H), 3.65 (s, 3H), 2.64 (ddd, J_1 = 17.5 Hz, J_2 = 9 Hz, J_3 = 1.7 Hz 1H), 2.05 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): δ CH_3: 51.6, 27.7, 24.9, 21.4, 20.4, 19.3, 18.5, 16.5; CH_2: 35.2, 33.1, 32.7, 31.9, 31.2, 30.6, 24.3, 23.6, 22.1; CH_1: 80.2, 54.8, 48.7, 33.0; CH_0: 213.2, 174.5, 170.9, 147.2, 132.8, 64.2, 49.1, 44.9, 40.2. HRMS (ESI): m/z calcd for $C_{30}H_{46}O_5Na^+$ $[M + Na]^+$ 509.32375, found 509.32394.

*(R)-Methyl 4-((3aS,3bS,5aS,7S,9aS,10aR,11aR)-7-Acetoxy-3a,3b,6,6,9a-pentamethyl-10-oxo-3a,3b,4,5,5a,6,7,8,9,-9a,10,10a,11,11a-tetradecahydro-3H-benzo[f]cyclopenta[a]-azulen-1-yl)pentanoate (**12**).* White foam. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.15 (m, 1H), 4.46 (dd, J_1 = 11.8 Hz, J_2 = 4.4 Hz, 1H), 3.65 (s, 3H), 3.41 (dd, J_1 = 12.2 Hz, J_2 = 6.4 Hz, 1H), 2.72 (dd, J_1 = J_2 = 8.3 Hz, 1H), 2.37 (dd, J_1 = 17.2 Hz, J_2 = 2.2 Hz, 1H), 2.05 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.70 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): δ CH_3: 51.7, 27.7, 27.3, 23.4, 21.4, 18.6, 18.1, 16.5; CH_2: 40.7, 37.7, 31.5, 31.2, 30.3, 28.3, 23.58, 23.57; CH_1: 122.4, 80.1, 57.7, 52.6, 50.9, 31.9; CH_0: 213.7, 174.6, 170.8, 150.6, 56.2, 49.3, 47.6, 40.2. HRMS (ESI): m/z calcd for $C_{30}H_{46}O_5Na^+$ $[M + Na]^+$ 509.32375, found 509.32385.

Chromatographic Separation of the Mixture of 7 and 9−12. A column was packed with 50 g of silica, and the mixture of ethyl acetate and hexanes (10/90) as a mobile phase. A mixture (100 mg) containing **7** and **9−12** was loaded on the column in a minimum amount of DCM, followed by the gravity elution with the mixture of ethyl acetate and hexanes (10/90). Compound **9** was eluted first as a transparent oil (10 mg, 10%), R_f = 0.34 (EA/hex = 20/80), followed by the elution of compound **11** as a transparent oil (6.1 mg, 6%), R_f = 0.31 (EA/hex = 20/80). The elution of an inseparable mixture of **7**,

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10, and **12** (76 mg, 76%), R_f = 0.30 (EA/hex = 20/80) completed the separation. A mixture of compounds **7**, **10**, and **12** (20 mg) was further separated by semipreparative HPLC (Agilent C18 column 21.2 × 250 mm, isocratic elution CH_3CN/H_2O = 80/20, flow rate 5 mL/min) to yield **7** as a white foam (4.5 mg, 23%), t_R = 98.9 min, **10** as a white foam (5 mg, 25%), t_R = 110.1 min; and **12** as a white foam (3.7 mg, 19%), t_R = 122.0 min.

■ ASSOCIATED CONTENT

Supporting Information

General experimental details, complete reference 26, ^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; HMQC, HMBC, COSY, and NOESY NMR spectra and the key COSY, HMBC, and NOESY correlations of compounds **5**−**12**; HPLC chromatogram of the separation of **7**, **10**, and **12**. 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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