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Molecular Library Synthesis Using Complex Substrates: Expanding the Framework of Triterpenoids

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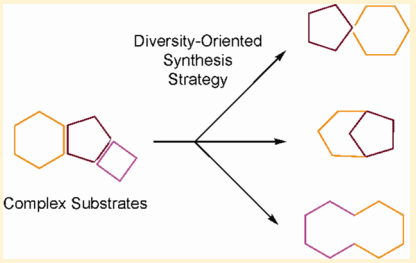
Supporting Information

ABSTRACT: The remodeling of a natural product core framework by means of diversity-oriented synthesis (DOS) is a valuable approach to access diverse/biologically relevant chemical space and to overcome the limitations of combinatorial-type compounds. Here we provide proof of principle and a thorough conformational analysis for a general strategy whereby the inherent complexity of a starting material is used to define the regio- and stereochemical outcomes of reactions in chemical library construction. This is in contrast to the traditional DOS logic employing reaction development and catalysis to drive library diversity.



INTRODUCTION

The construction of combinatorial libraries coupled with high-throughput screening has been a primary engine of the drug discovery process over the past three decades.[1,2] A central tenet of this scientific model is that such libraries confer a massive number of diverse chemical entities and drug leads.[3] Because of this reliance on library-derived molecules, natural products, despite their long history of success in pharmaceutical research,[4,5] have seen a decline in drug discovery efforts.[6,7] The subsequent realization that combinatorial-type molecules are substantially less diverse in their chemical structures as compared to molecules from natural sources[8,9] has led to the syntheses around "privileged scaffolds",[10−13] chemical alteration of crude natural product extracts,[14−17] and diversity-oriented synthesis (DOS), which was introduced to construct complex and diverse molecular skeletons from simple and similar starting materials.[18−21]

The synthetic approaches for the aforementioned library types have generally followed the traditional logic of organic synthesis: generating libraries of complex molecules from simple substrates using new reaction development and/or catalysis. The approach we illustrate herein deviates from this traditional model in that we set out to identify chemical functionality that can be exploited to rearrange the carbocyclic skeleton of an abundant natural product. The central hypothesis behind our approach was that instead of relying on reaction development and catalysis to impart stereochemical and regiochemical selectivity, we postulated that the inherent complexity of the natural product-derived substrates can drive stereoselective and regioselective reactions. Herein we provide proof of principle for this concept. While a number of studies have produced novel scaffolds using the rearrangement of functionalities embedded within a natural product core structure,[22−27] this is the first report to carefully test and rationalize through conformational analysis the hypothesis that subtle perturbations to the structure of the parent natural product will have dramatic effects on the resultant products. Consequently, once a diversification strategy is devised, it can be applied to many members of a natural product family to afford significantly different resultant products. Coupled with a reliance on readily available natural products, we argue that this general concept will prove to be a powerful and transferable method for the development of diverse molecular libraries.

In this paper, we describe a synthetic strategy for remodeling a triterpenoid skeleton based on the reactivity patterns of lanosterol (Figure 1) and application of the devised strategy to a pentacyclic triterpenoid, bryonolic acid. Lanosterol was initially chosen because of the unsaturated B/C ring fusion, which was shown by the groups of Snatzke,[28] Fox,[29] Sicinski,[30,31] and Marsaioli[32,33] to undergo iterative allylic oxidation/oxidative cleavage to produce transannular polyketones, followed by the aldol addition reactions to form distinct molecular skeletons. A literature search revealed that bryonolic acid is the major documented pentacyclic triterpenoid with the unsaturated B/C ring fusion.[34] We hypothesized that based on this structural similarity, bryonolic acid will react in a complementary fashion producing novel pentacyclic triterpenoids, each distinctively different from the others and the prototype structure. In addition, bryonolic acid can be isolated in gram-quantities from the sprouts of *Cucurbita pepo L.* (common zucchini)[35] and is known to have anti-inflammatory properties.[36]

RESULTS AND DISCUSSION

Substrate **3** was prepared via methylation of C-29 carboxylic acid of bryonolic acid **1** with diazomethane to initially form ester **2**, followed by the protection of the hydroxyl group at C3 to generate acetate **3** (Scheme 1).

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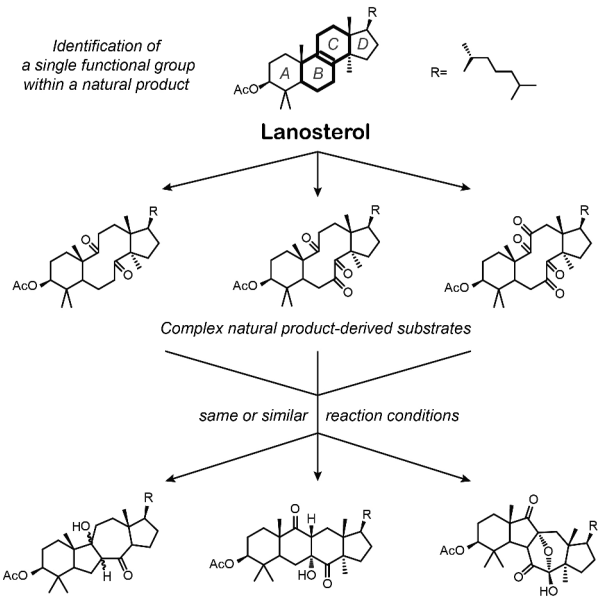
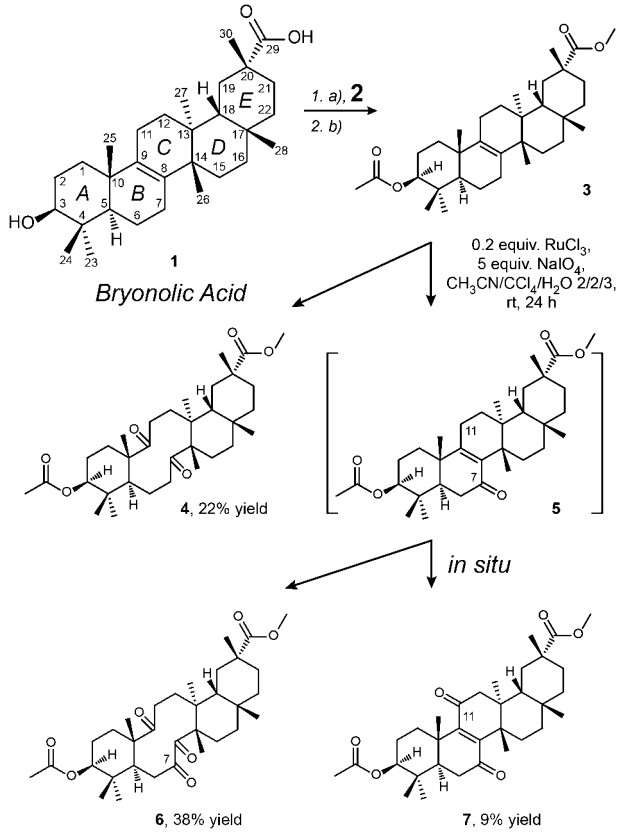


Figure 1. Diversity-oriented synthesis strategy based on the reactivity patterns of lanosterol.

Scheme 1. Oxidation of the Double Bond at the B/C Ring Fusion of the Substrate 3[a]

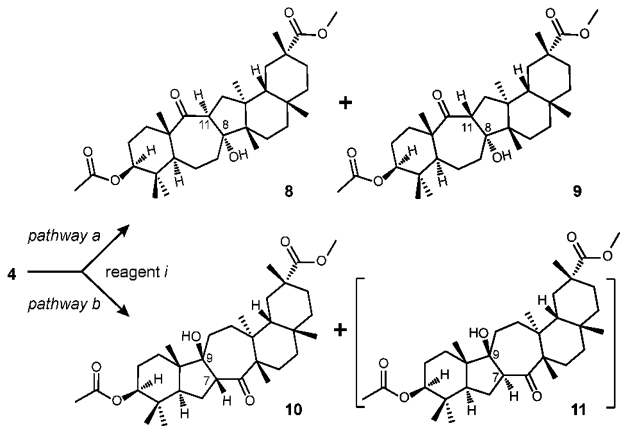


[a]Key: (a) CH_2N_2, THF, rt for 5 min (**2**, 88% yield); (b) $(CH_3CO)_2O$, pyridine, 50 °C for 24 h (**3**, 84% yield).

In order to gain access to ketones **4** and **6**, protected bryonolic acid **3** was subjected to catalytic oxidation with ruthenium tetroxide under Sharpless conditions.[37] Under these conditions, substrate **3** underwent competing oxidative cleavage of Δ8,9 double bond to form the desired diketone **4** and regioselective allylic oxidation at C7 to give α,β-unsaturated ketone **5** (Scheme 1). This transformation was fast and robust providing the complete conversion of starting material in 20 min as detected by TLC. However, with an extended reaction time (24 h), intermediate **5** was further oxidized in situ by ruthenium tetroxide to give the desired triketone **6** and the product of competing CH activation **7**.

Transannular aldol addition of diketone **4** was next investigated[38−41] (Table 1). Examination of the structure of

Table 1. Aldol Addition of Diketone 4 via Pathways a and b



		isolated yield (%)			
entry	reagent *i*[a]	**8**	**9**	**10**	**11**
1	TFA	45	0	40	0
2	NaH	56	0	6	0
3	pyrrolidine	80	0	8	0
4	LDA	71	0	22	0
5	LiHMDS	65	0	25	0
6	LiTMP	48	0	43	0
7	Ph_3CLi	79	0	5	0
8	Al_2O_3	81	7	0	0
9	$TiCl_4$	50	0	32	0

[a]See the Experimental Section for detailed experimental procedures.

diketone **4** reveals two possible enolization sites, potentially leading to four different regioisomeric aldol adducts (pathways a and b). Since aldol addition is one of the most well-known reactions in organic synthesis,[42,43] our initial efforts were focused on the standard aldol protocols. The use of catalytic TFA at room temperature led to the formation of the mixture of *syn* product of pathway a (**8**) and the *syn* product of pathway b (**10**) in good overall yield (85%, Table 1, entry 1). The use of sodium hydride as well as pyrrolidine as an organocatalyst for enamine-mediated aldol reaction gave a similar distribution of products **8** and **10**, although reaction with sodium hydride led to some degradation (Table 1, entries 2 and 3). Predominant formation of aldol adduct **8** suggested that it was the more thermodynamically stable product of the reaction. It is noteworthy that no products of aldol condensation were observed.

Our next step was to force the transannular aldol reaction of diketone **4** into pathway b under the kinetic conditions. Upon reaction of diketone **4** with LDA (1.1 equiv, THF, −78 °C to rt), aldol adducts **8** and **10** were formed in 71% and 22% yield, respectively (Table 1, entry 4). The increase in the steric bulk of the amide base led to the increased formation of aldol adduct **10**. Thus, the use of LiHMDS produced **10** in 25% yield and

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LiTMP proved to be the reagent of choice, giving the highest yield of aldol adduct **10** (43%, Table 1, entry 6).

However, upon treatment of diketone **4** with Al_2O_3 (basic) in DCM, aldol adduct **8** was isolated in 81% yield but **10** was not observed. Instead, the *anti* product of pathway a (**9**) was formed in 7% yield (Table 1, entry 8). By the virtue of substrate bias, the lowest energy conformation of the cyclodecane ring of diketone **4** is "boat (with bow at C-5 and stern between C-8 and C-11) -chair−chair" which determines the α-face position of the carbonyl group at C-8 and β-face position of the carbonyl at C-9 (Figure 2). In both pathways a and b, the pseudoaxial α-

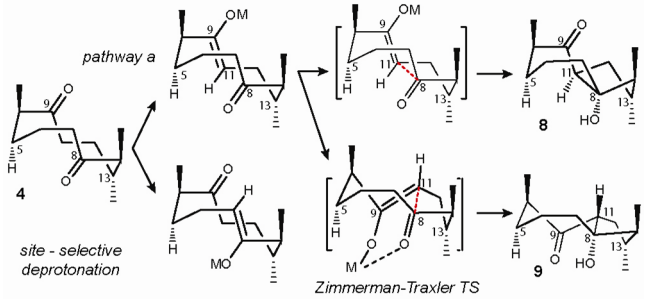


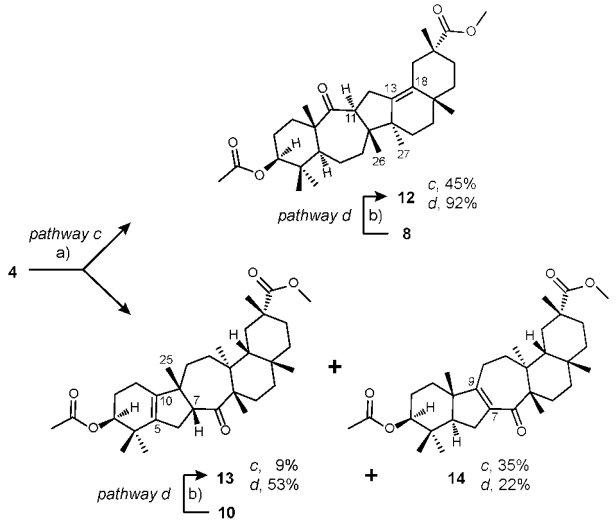
Figure 2. Working model demonstrates the role of the enolate geometry and the conformation of cyclodecane ring of diketone **4** toward stereoselectivity.

hydrogen is antiperiplanar with the carbonyl and the pseudoequatorial α-hydrogen is orthogonal to the C=O bonds, thus producing the *trans* (*Z*)-enolate of diketone **4** as the key intermediate after deprotonation by the loss of the pseudoequatorial hydrogen. The intermediate enolate is geometrically predisposed for the formation of transannular C−C bond with *syn* configuration at the ring junction. To rationalize the formation of *anti* product **9**, we hypothesized that when treated with a Lewis acid such as Al_2O_3, the key intermediate engages in the Zimmerman−Traxler transition state[44] (Figure 2) which determines the β-face position of H-11 and α-face position of the keto group at C-9. When purified aldol adduct **8** was resubjected to the same reaction conditions (100 equiv Al_2O_3, DCM, rt, 16 h), no interconversion of these products was observed. The absence of product interconversion under the same set of conditions led to a conclusion that the relative stereochemistry of *anti* product **9** is the result of Lewis acid-controlled transition state of the aldol addition reaction of the diketone **4**.

It is worth noting that the lithium cation, which is generally known to follow the Zimmerman−Traxler model, did not give any *anti* products in reactions with amide bases (Table 1, entries 4−6). The reaction of diketone **4** with $TiCl_4$ in the presence of tertiary amine (1.1 equiv, −78 °C to rt) led to the formation of aldol adducts **8** and **10** in 1.6:1 ratio and no *anti* products were observed (Table 1, entry 9). In due course, treatment of diketone **4** with $BF_3{\cdot}Et_2O$ (1.1 equiv, −78 °C to rt) unexpectedly gave aliphatic ketones **12** and **13** and α,β-unsaturated ketone **14** (Scheme 2, pathway c).

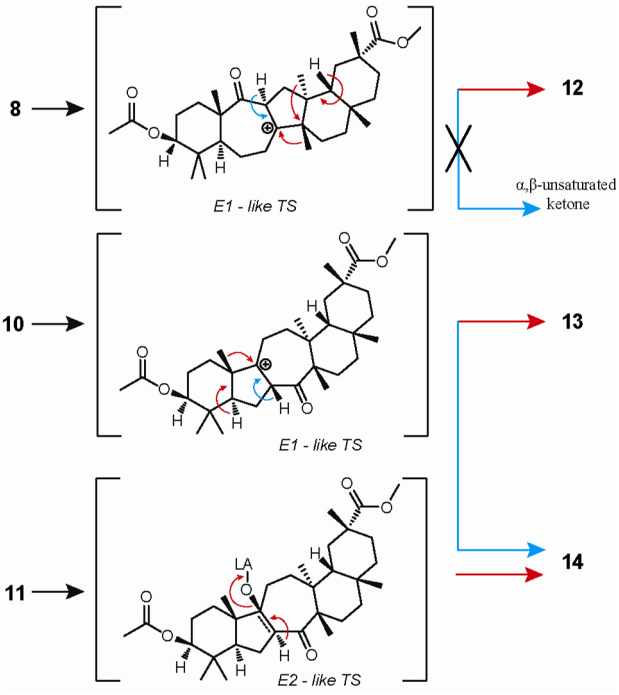
The absolute stereochemistry of H-11 suggested that ketone **12** was the result of aldol addition via pathway a to form aldol adduct **8** followed by a cascade of methide shifts and an elimination of H-18 to form internal double bond at Δ13,18 (Scheme 3). The control experiment (Scheme 2, pathway d) confirmed our prediction when isolated aldol adduct **8** was treated with $BF_3{\cdot}Et_2O$ to form aliphatic ketone **12** in 92% yield.

Scheme 2. Aldol Addition/Condensation of Diketone 4 via Pathways c and d[a]



[a]Key: (a) $BF_3{\cdot}Et_2O$ (1.1 equiv), DCM, −78 °C to rt, 4 days; (b) $BF_3{\cdot}Et_2O$ (10 equiv), DCM, −78 °C to rt, 18 h.

Scheme 3. Mechanistic Considerations for the Formation of Ketones 12, 13, and 14 from the Corresponding Aldol Adducts 8, 10, and 11



Thermodynamic stability of **8** and *trans* arrangement of the C-8 hydroxyl group and the methyl at C-26 add to the robustness of this transformation. A similar rationale was then proposed for the formation of ketones **13** and **14** via pathway c in 1:4 ratio. β-Facial position of H-7 in ketone **13** predisposed for the formation of aldol adduct **10** via pathway b to be followed by either a C-25 methide shift or an elimination of H-7 through a common carbocationic intermediate and E1-type transition state to yield ketones **13** or **14**, respectively.

Both of these possibilities seem equally plausible due to the fact that both the C-25 methyl group and the H-7 are in *cis*

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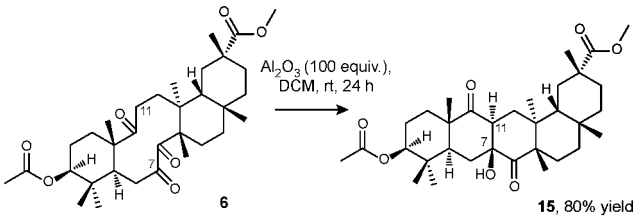
arrangement with the hydroxyl group at C-9. The control experiment (Scheme 2, pathway d) with isolated aldol adduct **10** yielded compounds **13** and **14** in 2.4:1 ratio. The reversal of selectivity observed for the production of ketone **13** over **14** via pathway d led to the conclusion that the reaction through pathway c gives intermediately aldol adduct **10** and an *anti* product of pathway b (**11**), which has the antiperiplanar arrangement of H-7 and the hydroxyl group at C-9 (Scheme 3), thus raising the possibility of the increased production of ketone **14**, if the overall elimination of water is to occur through E2-type transition state.

In the case of triketone **6** (Scheme 4), we also located the lowest energy conformation, the cyclodecane part of which

Scheme 4. Aldol Addition Reaction of Triketone 6



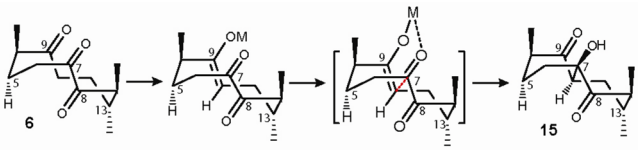
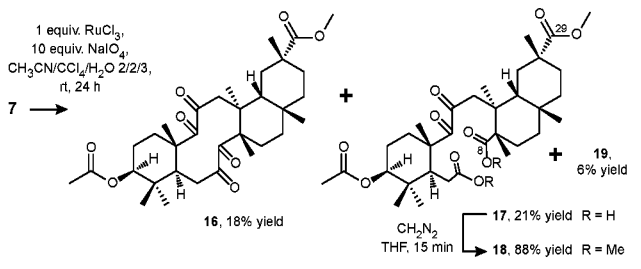


Figure 3. Working model demonstrates the role of the enolate geometry and the conformation of cyclodecane ring of triketone **6** toward stereoselectivity.

closely resembles that of diketone **4** (Figure 3). Abstraction of pseudoequatorial α-hydrogen at C-11 upon treatment of triketone **6** with Al_2O_3 in DCM at room temperature produces trans (Z)-enolate, which is structurally biased to adopt the Zimmerman–Traxler transition state with C-7 carbonyl, thus forming *anti* product **15**.

In an attempt to obtain the last transannular polyketone in the desired series, we performed the oxidative cleavage of the enone **7** (Scheme 5). As in the case of protected bryonolic acid **3**, ruthenium tetroxide under Sharpless conditions proved to be the reagent of choice for this otherwise hardly achievable transformation. However, larger amounts of ruthenium catalyst and reoxidant and a longer reaction time were required to afford, after careful column chromatography, tetraketone **16**

Scheme 5. Oxidative Cleavage of 7 with Ruthenium Tetroxide under Sharpless Conditions

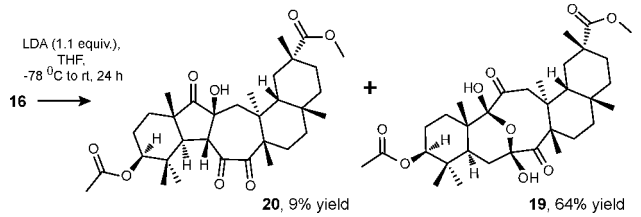


together with the product of oxidative destruction **17** in 18% and 21% yield, respectively.

The structure of the carboxylic acid **17** was tentatively suggested after a thorough NMR study but appeared to be difficult to establish due to slow conformational equilibrium and identical chemical shifts of C-8 and C-29 carbonyls at 179.5 ppm. The structure was established unambiguously after carboxylic acid **17** was treated with diazomethane to form the ester **18**, which showed three singlets centered around 3.6 ppm in ^1H spectrum as well as four ester carbonyls and two keto groups in the ^{13}C spectrum.

In order to obtain the final aldol adduct in the proposed molecular library, tetraketone **16** was treated with LDA (1.1 equiv, THF, −78 °C to rt) to give the aldol adduct **20** and the product of transannular hemiketalization **19** in 9% and 64% yield, respectively (Scheme 6). As expected, tetraketone **16** was not deprotonated at C-12 since it is considerably more sterically hindered as compared to C-6.

Scheme 6. Aldol Addition Reaction of Tetraketone 16



In the ground-state conformation[46] of tetraketone **16**, pseudoaxial H-6 is coplanar with the carbonyl at C-7, giving rise to the cis (*E*)-enolate as the key intermediate upon the abstraction of pseudoequatorial H-6 by the base (Figure 4).

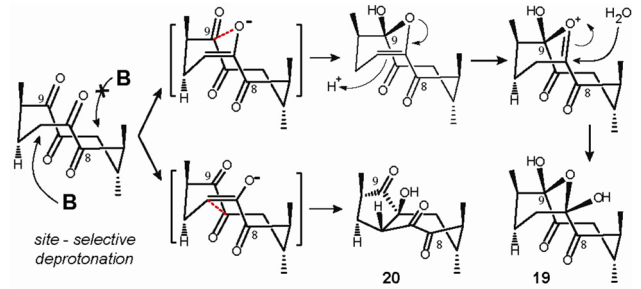


Figure 4. Working model demonstrates the role of the enolate geometry and the conformation of cyclodecane ring of tetraketone **16** toward regio- and stereoselectivity.

The higher yield of **19** over the aldol adduct **20** can be explained in view of the fact that the transition state leading to the aldol adduct **20** seems to be markedly higher in energy in contrast with the transition state leading to the product of transannular hemiketalization **19**. The formation of **19** suggests a mechanism which presumably proceeds through an intermediate with the charge localized on the oxygen of the pyranyl ring,[45] thereby bringing a novel triterpenoid structure into the library by virtue of an unanticipated reaction. This proposed mechanism was confirmed when the reaction was quenched with D_2O, resulting in a partial deuterium incorporation at C-6.

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CONCLUSION

Here we have illustrated what we consider to be a new principle in the construction of molecular libraries. We have shown a strategy for the remodeling of the triterpenoid skeleton devised on the basis of the reactivity of the steroidal triterpenoid lanosterol. We hypothesized that the subtle differences between the steroid and triterpeoid core structures would impart differential reactivity. This hypothesis was confirmed by illustrating that despite the common unsaturation at the B/C-ring fusion, the differences between the parent molecules led to dramatic differences in reactivity and, concomitantly, the composition of the resultant chemical library. Specifically, the aldol addition of diketone **4** was shown to follow three different pathways. Moreover, the aldol reactivity of the tetraketone **16** appeared to be completely different from that derived from lanosterol, giving rise to the novel bridged structure **19** as a major reaction product. We would argue that the strategy outlined here is a general approach that could be applied to a wide range of natural product families, allowing access to broad categories of novel and potentially biologically relevant molecules that would be otherwise very difficult to attain.

EXPERIMENTAL SECTION

(2*R*,4a*S*,6a*S*,8a*R*,10*S*,12a*S*,14a*S*,14b*R*)-10-Hydroxy-2,4a,-6a,9,9,12a,14a-heptamethyl-1,2,3,4,4a,5,6,6a,7,8,8a,9,-10,11,12,12a,13,14,14a,14b-icosahydropicene-2-carboxylic Acid (1). Bryonolic acid (**1**) was isolated in gram quantities from the sprouts of "Spineless beauty" zucchini squash by previously published method:[35] mp 274−278 °C (lit.[35] mp 274−278 °C).

(2*R*,4a*S*,6a*S*,8a*R*,10*S*,12a*S*,14a*S*,14b*R*)-Methyl 10-Hydroxy-2,4a,6a,9,9,12a,14a-heptamethyl-1,2,3,4,4a,5,6,6a,7,8,8a,9,10,-11,12,12a,13,14,14a,14b-icosahydropicene-2-carboxylate (2). In a round-bottom flask open to atmosphere, bryonolic acid (**1**) (3 g, 6.57 mmol) was dissolved in 65 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 until full conversion detected by TLC (approximately 5 min). The reaction was quenched by dropwise addition of glacial acetic acid until the yellow color of the solution disappeared. The reaction mixture was concentrated under vacuum and the crude product was purified by column chromatography on silica to give **2** as a white solid (2.72 g, 88%). Mp: 142−144 °C. R_f = 0.5 (EA/hex, 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.61 (s, 3H), 3.23 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 2.37 (d, J = 12 Hz, 1H), 2.19 (m, 1H), 2.1 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.79 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 179.4, 134.1, 133.9, 79.0, 51.6, 50.5, 44.8, 41.9, 40.5, 38.9, 37.6, 37.2, 37.1, 35.1, 34.5, 33.0, 31.3, 31.0, 30.9, 30.4, 30.0, 28.1, 27.9, 27.7, 25.1, 22.1, 20.8, 20.0, 19.3, 17.2, 15.7. HRMS (EI): m/z calcd for $C_{31}H_{50}O_3^+$ $[M]^+$ 470.37600, found 470.37553.

(2*R*,4a*S*,6a*S*,8a*R*,10*S*,12a*S*,14a*S*,14b*R*)-Methyl 10-Acetoxy-2,4a,6a,9,9,12a,14a-heptamethyl-1,2,3,4,4a,5,6,6a,7,8,8a,9,10,-11,12,12a,13,14,14a,14b-icosahydropicene-2-carboxylate (3). In a round-bottom flask, bryonolic acid methyl ester **2** (2.35 g, 5 mmol) was dissolved in 10 mL of dry pyridine. Acetic anhydride (1.02 g, 10 mmol) was added to the resulting solution by a quick syringe transfer. The reaction mixture was stirred at 50 °C for 24 h, after which time pyridine was removed at reduced pressure and the crude mixture was taken into ethyl acetate. The organic layer was washed successively with dilute HCl, water and saturated solution of sodium bicarbonate. It was subsequently dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography to give **3** as a white solid (2.16 g, 84%). Mp: 164−167 °C. R_f = 0.62 (EA/hex =3/7). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.47 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.62 (s, 3H), 2.37 (d, J = 16 Hz, 1H), 2.19 (d, J = 12 Hz, 1H), 2.05 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H), 0.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 179.3, 171.1, 134.1, 134.0, 81.0, 51.7, 50.7, 44.9, 41.9, 40.6, 37.8, 37.5, 37.3, 37.1, 34.8, 34.5, 33.0, 31.3, 31.0, 30.9, 30.4, 30.0, 28.1, 27.5, 25.1, 24.3, 22.2, 21.5, 20.8, 20.1, 19.2, 17.1, 16.8. HRMS (EI): m/z calcd for $C_{33}H_{52}O_4^+$ $[M]^+$ 512.38656, found 512.38532.

Preparation of 4, 6, and 7. In a 200 mL single-neck round-bottom flask, $RuCl_3$ (81 mg, 0.39 mmol) was added in one portion to the solution of $NaIO_4$ (2.09 g, 9.75 mmol) in 59 mL of H_2O, and the resulting suspension was stirred open to atmosphere for 15 min, followed by the addition of 39 mL of acetonitrile. The solution of **3** (1 g, 1.95 mmol) in 39 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 24 h, at which time 10 mL of ethanol 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 products further separated by chromatography. Silica column chromatography yielded an inseparable mixture (351 mg) of **4** and **7**, R_f = 0.45 (EA/hex =25/75), and pure **6** as a yellow solid (416 mg, 38%). Mp: 168−171 °C. R_f = 0.38 (EA/hex =25/75). Compounds **4** and **7** were further separated by semiprep HPLC (Agilent C18 column 21.2 × 250 mm, isocratic elution CH_3CN/H_2O = 9/1, flow rate 5 mL/min) to yield **7** as a yellow oil (96 mg, 9%), t_R = 52 min, and **4** as white foam (231 mg, 22%), t_R = 66 min.

(2*R*,4a*S*,6a*S*,9a*S*,11*S*,13a*S*,16a*S*,16b*R*)-Methyl 11-Acetoxy-2,4a,6a,10,10,13a,16a-heptamethyl-7,14-dioxodocosahydrobenzo[6,7]cyclodeca[1,2-*a*]naphthalene-2-carboxylate (4). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.61 (m, 1H), 3.67 (s, 3H), 2.65−2.57 (2H), 2.39 (d, J = 16 Hz, 1H), 2.22 (d, J = 16 Hz, 1H), 2.08 (s, 3H), 1.174 (s, 3H), 1.170 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 218.1, 216.6, 179.0, 171.1, 80.2, 54.1, 52.2, 52.0, 45.52, 45.51, 44.2, 40.8, 38.7, 36.4, 36.3, 35.2, 34.7, 32.9, 31.7, 31.6, 31.5, 29.83, 29.79, 29.2, 28.5, 28.4, 28.1, 23.5, 21.4, 19.3, 17.4, 16.4, 16.0. HRMS (EI): m/z calcd for $C_{33}H_{52}O_6^+$ $[M]^+$ 544.37639, found 544.37685.

(2*R*,4a*S*,6a*S*,9a*S*,11*S*,13a*S*,16a*S*,16b*R*)-Methyl 11-Acetoxy-2,4a,6a,10,10,13a,16a-heptamethyl-7,8,14-trioxodocosahydrobenzo[6,7]cyclodeca[1,2-*a*]naphthalene-2-carboxylate (6). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.67 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.67 (s, 3H), 2.78 (dd, J_1 = 20 Hz, J_2 = 8 Hz, 1H), 2.71 (dd, J_1 = 16 Hz, J_2 = 4 Hz, 1H), 2.32 (d, J = 16 Hz, 1H), 2.27 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 2.23 (d, J = 12 Hz, 1H), 2.06 (s, 3H), 1.79 (dd, J_1 = 16 Hz, J_2 = 4 Hz, 1H), 1.73 (dd, J_1 = 16 Hz, J_2 = 8 Hz, 1H), 1.54 (d, J = 8 Hz, 1H), 1.25 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 214.1, 212.6, 203.1, 179.2, 171.0, 79.6, 53.1, 52.0, 50.7, 46.3, 44.4, 43.5, 40.8, 39.3, 39.2, 35.4, 33.6, 33.0, 32.3, 31.9, 31.8, 31.7, 31.2, 30.9, 29.6, 28.5, 27.5, 23.4, 21.4, 17.6, 16.9, 16.6, 16.1. HRMS (ESI): m/z calcd for $C_{33}H_{50}O_7Na^+$ $[M + Na]^+$ 581.3454, found 581.3465.

(2*R*,4a*S*,6a*S*,8a*R*,10*S*,12a*S*,14a*S*,14b*R*)-Methyl 10-Acetoxy-2,4a,6a,9,9,12a,14a-heptamethyl-7,13-dioxo-1,2,3,4,4a,5,6,-6a,7,8,8a,9,10,11,12,12a,13,14,14a,14b-icosahydropicene-2-carboxylate (7). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.56 (m, 1H), 3.66 (s, 3H), 2.58 (ddd, J_1 = 12 Hz, J_2 = J_3 = 4 Hz, 1H), 2.51−2.47 (3H), 2.07 (s, 3H), 1.93 (ddd, J_1 = J_2 = 12 Hz, J_3 = 4 Hz, 1H), 1.28 (s, 3H), 1.24 (s, 3H), 1.20 (s, 3H), 1.06 (s, 3H), 0.989 (s, 3H), 0.987 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 200.0, 199.8, 179.1, 171.1, 154.9, 152.7, 79.6, 52.1, 52.0, 48.1, 44.2, 42.1, 40.5, 39.1, 38.1, 37.6, 36.8, 36.3, 34.1, 33.6, 32.5, 31.0, 30.9, 30.6, 29.8, 29.6, 27.5, 25.3, 23.9, 21.4, 21.0, 20.6, 17.9, 16.1. HRMS (ESI): m/z calcd for $C_{33}H_{48}O_6Na^+$ $[M + Na]^+$ 563.3348, found 563.3352.

Preparation of 8−10. *Table 1 (Entry1).* In a round-bottom flask open to atmosphere, trifluoroacetic acid (1 μL, 35 mol %) was added to the solution of **4** (20 mg, 0.0367 mmol) in 1 mL of DCM. The flask was sealed with a glass stopper, and the mixture was stirred vigorously for 72 h, at which time the solvent was removed in vacuo, and the mixture of products was separated by column chromatography on silica without additional workup to yield **8** (9 mg, 45%) and **10** (8 mg, 40%).

Table 1 (Entry 2). NaH (95%, 2 mg, 0.0792 mmol) was placed in a flame-dried (under vacuum) round-bottom flask, followed by the addition of 0.5 mL of dry THF. The resulting suspension was cooled to 0 °C, and the solution of **4** (36 mg, 0.066 mmol) in 0.5 mL of dry

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THF was added dropwise at this temperature. The reaction mixture was stirred at 0 °C for 30 min and then warmed to rt and stirred at rt for 19 h, at which time the solvent was removed in vacuo, the crude mixture was treated with 5% acetic acid in H_2O, 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 **8** (20 mg, 56%) and **10** (2 mg, 6%).

Table 1 (Entry 3). To a solution of **4** (25 mg, 0.0459 mmol) in 0.5 mL of DCM in a flame-dried (under vacuum) round-bottom flask was added pyrrolidine (1.9 μL, 1.63 mg, 0.023 mmol) dropwise at rt. The resulting mixture was stirred at that temperature for 24 h, at which time the solvent was removed under vacuum and the crude mixture of products was separated by column chromatography on silica without additional workup to give **8** (20 mg, 80%) and **10** (2 mg, 8%).

General Procedure for Reaction of 4 with Amide Bases. The solution of a secondary amine (1.1 equiv) in dry THF (0.027 M in amine) 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, 1.1 equiv). The reaction mixture was warmed to 0 °C, stirred at this temperature for 5 min, and subsequently cooled to −78 °C. A solution of **4** (1 equiv) in dry THF (0.07 M in 4) was then added dropwise to the solution of lithium amide by syringe at −78 °C. The reaction mixture was allowed to warm to rt overnight and stirred at rt for a total of 24 h. After the solvent was removed in vacuo, the residue was taken up in DCM and washed with water and brine, and the organic layer was dried over Na_2SO_4. Evaporation of the solvent in vacuo gave crude product mixtures that were further separated by chromatography.

Table 1 (Entry 4). Following the general procedure, the use of diisopropylamine (20 mg, 29 μL, 0.202 mmol), *n*-butyllithium (0.202 mmol, 81 μL), **4** (100 mg, 0.1836 mmol), and THF (10 mL) gave, after column chromatography on silica, **8** (71 mg, 71%) and **10** (22 mg, 22%).

Table 1 (Entry 5). Following the general procedure, the use of hexamethyldisilazane (6.5 mg, 8.5 μL, 0.0404 mmol), *n*-butyllithium (0.0404 mmol, 16.2 μL), **4** (20 mg, 0.0367 mmol), and THF (2 mL) gave, after column chromatography on silica, **8** (13 mg, 65%) and **10** (5 mg, 25%).

Table 1(Entry 6). Following the general procedure, the use of 2,2,6,6-tetramethylpiperidine (5.7 mg, 0.0404 mmol), *n*-butyllithium (0.0404 mmol, 16.2 μL), **4** (20 mg, 0.0367 mmol), and THF (2 mL) gave, after column chromatography on silica, **8** (9.6 mg, 48%) and **10** (8.6 mg, 43%).

Table 1 (Entry 7). Following the general procedure for amide bases, the use of Ph_3CH (9.9 mg, 6.9 μL, 0.0404 mmol), *n*-butyllithium (0.0404 mmol, 16.2 μL), **4** (20 mg, 0.0367 mmol), and THF (2 mL) gave, after column chromatography on silica, **8** (16 mg, 79%) and **10** (1 mg, 5%).

Table 1 (Entry 8). A round-bottom flask open to atmosphere was charged with basic alumina (1.9 g, 18.4 mmol), followed by the addition of DCM (1 mL). A solution of **4** (100 mg, 0.184 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 16 h, at which time the mixture 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 an inseparable mixture (90 mg) of **8** and **9**: R_f = 0.4 (EA/hex =25/75). Compounds **8** and **9** were further separated by semiprep HPLC (Agilent C18 column 21.2 × 250 mm, isocratic elution CH_3CN/H_2O = 95/5, flow rate 5 mL/min) to yield **8** (81 mg, 81%), t_R = 53 min, and **9** (7 mg, 7%), t_R = 68 min.

Table 1 (Entry 9). Dry DCM (1 mL) was added to a flame-dried (under vacuum) round-bottomed flask. The flask was cooled to −78 °C, and $TiCl_4$ (41.8 mg, 0.22 mmol, 24.2 μL) was added at that temperature by a quick syringe transfer, followed by a dropwise addition of diisopropylethylamine (33.2 mg, 0.257 mmol, 44.8 μL). A solution of **4** (100 mg, 0.1836 mmol) in dry DCM (1 mL) was added to the reaction mixture at −78 °C, and the reaction mixture was allowed to warm to rt and stirred at rt for 24 h, at which time 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 **8** (49.5 mg, 50%) and **10** (31.5 mg, 32%).

(2*R*,4a*S*,6a*S*,6b*R*,8a*S*,10*S*,12a*S*,13a*S*,14a*S*,14b*R*)-Methyl 10-Acetoxy-6b-hydroxy-2,4a,6a,9,9,12a,14a-heptamethyl-13-oxodocosahydrobenzo[*f*]naphtho[2,1-*a*]azulene-2-carboxylate (8). White solid. Mp: 235−238 °C. R_f = 0.53 (EA/hex =3/7). R_f = 0.4 (EA/hex =25/75). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.45 (m, 1H), 3.62 (s, 3H), 3.57 (dd, $J_1 = J_2$ = 12 Hz, 1H), 2.43 (dd, J_1 =12.6 Hz, J_2 = 4.2 Hz, 1H), 2.17 (2H), 2.04 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.59 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 215.4 (CO), 179.3 (CO), 171.0 (CO), 84.5 (COH), 80.2 (CH), 56.8 (CH), 52.8 (C), 51.8 (CH_3), 49.6 (C), 46.8 (C), 46.0 (CH), 44.1 (CH), 40.7 (C), 38.5 (CH_2), 37.8 (C), 37.4 (CH_2), 35.9 (CH_2), 34.9 (CH_2), 33.0 (CH_2), 32.7 (CH_3), 31.4 (C), 31.1 (CH_3), 30.6 (CH_2), 30.3 (CH_2), 27.8 (CH_3), 24.0 (CH_2), 23.7 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 19.7 (CH_2), 17.8 (CH_3), 16.6 (CH_3), 16.1 (CH_3). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{52}O_6Na^+$ $[M + Na]^+$ 567.3661, found 567.3660.

(2*R*,4a*S*,6a*S*,6b*R*,8a*S*,10*S*,12a*S*,13a*R*,14a*S*,14b*R*)-Methyl 10-Acetoxy-6b-hydroxy-2,4a,6a,9,9,12a,14a-heptamethyl-13-oxodocosahydrobenzo[*f*]naphtho[2,1-*a*]azulene-2-carboxylate (9). White foam. R_f = 0.4 (EA/hex =25/75). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.48 (dd, J_1 =17.4 Hz, J_2 = 6 Hz, 1H), 3.70 (s, 3H), 3.60 (dd, J_1 =16.2 Hz, J_2 = 4.2 Hz, 1H), 2.35 (m, 1H), 2.04 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 212.4 (CO), 179.1 (CO), 170.8 (CO), 87.7 (COH), 80.4 (C), 53.3 (CH), 53.0 (C), 52.1 (CH_3), 49.5 (C), 48.5 (C), 47.1 (CH), 44.2 (CH), 40.7 (C), 40.0 (C), 37.6 (CH_2), 37.4 (CH_2), 35.8 (CH_2), 35.7 (CH_2), 32.8 (CH_2), 32.6 (CH_3), 32.3 (CH_2), 31.5 (C), 31.3 (CH_3), 30.2 (CH_2), 28.0 (CH_3), 24.2 (CH_2), 23.7 (CH_2), 23.5 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 21.2 (CH_3), 18.1 (CH_3), 16.4 (CH_3). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{52}O_6Na^+$ $[M + Na]^+$ 567.3661, found 567.3654.

(2*R*,4a*S*,6a*S*,7a*R*,8a*S*,10*S*,12a*S*,12b*S*,14a*S*,14b*R*)-Methyl 10-Acetoxy-12b-hydroxy-2,4a,6a,9,9,12a,14a-heptamethyl-7-oxodocosahydrobenzo[*a*]naphtho[2,1-*f*]azulene-2-carboxylate (10). White solid. Mp: 187−190 °C. R_f = 0.46 (EA/hex =3/7). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.45 (dd, J_1 = 12 Hz, J_2 = 4.8 Hz, 1H), 3.64 (s, 3H), 3.14 (d, *J* = 9.6 Hz, 1H), 2.42−2.38 (2H), 2.22 (d, *J* = 14.4 Hz, 1H), 2.16 (ddd, $J_1 = J_2$ = 14.4 Hz, J_3 = 4.8 Hz, 1H), 2.06 (ddd, $J_1 = J_2$ = 14.4 Hz, J_3 = 4.8 Hz, 1H), 2.05 (s, 3H), 1.84 (dd, $J_1 = J_2$ = 13.2 Hz, 1H), 1.75−1.47 (12H), 1.45 (s, 3H), 1.42−1.27 (4H), 1.18 (s, 3H), 1.13 (dd, J_1 = 13.8 Hz, J_2 = 6 Hz, 1H), 1.08 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 214.6 (CO), 179.2 (CO), 171.2 (CO), 82.1 (C), 81.0 (CH), 58.5 (CH), 56.3 (C), 52.0 (CH_3), 50.5 (CH), 49.7 (C), 45.7 (CH), 40.8 (C), 39.1 (C), 37.5 (C), 36.5 (CH_2), 34.0 (CH_2), 33.0 (CH_3), 32.8 (CH_2), 31.8 (C), 31.40 (CH_3), 31.35 (CH_2), 31.0 (CH_2), 30.8 (CH_2), 29.8 (CH_2), 29.0 (CH_3), 27.6 (CH_2), 25.0 (CH_2), 22.8 (CH_2), 21.4 (CH_3), 18.0 (CH_3), 17.8 (CH_3), 17.0 (CH_3), 16.1 (CH_3). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{52}O_6Na^+$ $[M + Na]^+$ 567.3661, found 567.3647.

Preparation of 12−14. Solution of **4** (30 mg, 0.055 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) (8.6 mg, 0.0605 mmol, 7.6 μL) at this temperature. The reaction mixture was allowed to warm to rt overnight and stirred at this temperature for a total of 4 days, 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 **13** as transparent oil (2.5 mg, 9%). R_f = 0.3 (EA/hex =15/85); **12** as white solid (13 mg, 45%). Mp: 214 °C. R_f = 0.27 (EA/hex =15/85). Compound **14** was obtained as a white solid (10 mg, 35%). Mp: 198−202 °C. R_f = 0.22 (EA/hex =15/85).

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(2*R*,4a*S*,6a*S*,6b*R*,8a*S*,10*S*,12a*S*,13a*S*)-Methyl 10-Acetoxy-2,4a,6a,6b,9,9,12a-heptamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,-8,8a,9,10,11,12,12a,13,13a,14-icosahydrobenzo[*f*]naphtha[2,1-*a*] azulene-2-carboxylate (12). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.52 (dd, J_1 = 10.2 Hz, J_2 = 6 Hz, 1H), 3.65 (dd, J_1 = J_2 = 9 Hz, 1H), 3.57 (s, 3H), 2.92 (dd, J_1 = 18 Hz, J_2 = 8.4 Hz, 1H), 2.74 (dd, J_1 = 13.8 Hz, J_2 = 2.4 Hz, 1H), 2.14 (dd, J_1 = 17.4 Hz, J_2 = 9.6 Hz, 1H), 2.05 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 0.99 (s, 6H), 0.96 (s, 3H), 0.89 (s, 3H), 0.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 217.4 (CO), 177.4 (CO), 171.0 (CO), 138.3 (C), 130.2 (C), 80.1 (CH), 51.5 (C), 51.33 (CH_3), 51.26 (CH), 50.7 (CH), 49.8 (C), 49.7 (C), 45.9 (C), 39.7 (CH_2), 38.8 (C), 36.8 (CH_2), 36.6 (CH_2), 36.1 (CH_2), 35.7 (CH_2), 34.1 (C), 32.2 (CH_2), 28.2 (CH_3), 28.1 (CH_3), 26.8 (CH_2), 25.1 (CH_2), 24.8 (CH_3), 23.7 (CH_2), 22.7 (CH_3), 21.8 (CH_2), 21.4 (CH_3), 19.0 (CH_3), 17.5 (CH_3), 16.9 (CH_3). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{50}O_5Na^+$ $[M + Na]^+$ 549.3556, found 549.3551.

(2*R*,4a*S*,6a*S*,7a*R*,10*S*,12b*R*,14a*S*,14b*R*)-Methyl 10-Acetoxy-2,4a,6a,9,9,12b,14a-heptamethyl-7-oxo-1,2,3,4,4a,5,6,6a,7,-7a,8,9,10,11,12,12b,13,14,14a,14b-icosahydrobenzo[*a*]-naphtho[2,1-*f*]azulene-2-carboxylate (13). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.75 (ddd, J_1 = 10.2 Hz, J_2 = 3 Hz, J_3 = 1.8 Hz, 1H), 3.58 (s, 3H), 3.32 (ddd, J_1 = 9 Hz, J_2 = 3 Hz, J_3 = 1.2 Hz, 1H), 2.96 (m, 1H), 2.42 (d, J = 15.6 Hz, 1H), 2.05 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.07 (s, 6H), 1.00 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 214.8 (CO), 179.1 (CO), 171.2 (CO), 137.5 (C), 137.3 (C), 78.2 (CH), 55.5 (C), 54.5 (CH), 51.8 (CH_3), 50.9 (C), 45.3 (CH), 40.7 (C), 39.4 (C), 36.7 (CH_2), 36.2 (C), 34.9 (CH_2), 32.9 (CH_3), 32.2 (CH_2), 31.8 (CH_2), 31.7 (CH_3), 31.5 (C), 31.4 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 27.0 (CH_2), 26.2 (CH_3), 25.6 (CH_3), 24.5 (CH_2), 21.6 (CH_3), 21.4 (CH_3), 19.7 (CH_2), 19.3 (CH_3), 17.5 (CH_3). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{50}O_5Na^+$ $[M + Na]^+$ 549.3556, found 549.3544.

(2*R*,4a*S*,6a*S*,8a*R*,10*S*,12a*S*,14a*S*,14b*R*)-Methyl 10-Acetoxy-2,4a,6a,9,9,12a,14a-heptamethyl-7-oxo-1,2,3,4,4a,5,6,6a,-7,8,8a,9,10,11,12,12a,13,14,14a,14b-icosahydrobenzo[*a*]-naphtho[2,1-*f*]azulene-2-carboxylate (14). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.52 (dd, J_1 = 11.4 Hz, J_2 = 4.8 Hz, 1H), 3.59 (s, 3H), 2.68 (dd, J_1 =15 Hz, J_2 = 6.6 Hz, 1H), 2.35 (d, J = 16.2 Hz, 1H), 2.05 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 206.9 (CO), 179.4 (CO), 171.1 (CO), 158.9 (C), 135.5 (C), 80.9 (CH), 56.2 (CH), 55.6 (C), 51.8 (CH_3), 50.8 (C), 46.1 (CH), 40.8 (C), 39.3 (C), 37.2 (C), 36.4 (CH_2), 34.0 (CH_2), 33.0 (CH_3), 32.7 (C), 32.6 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 31.3 (CH_3), 29.6 (CH_2), 29.3 (CH_2), 28.5 (CH_3), 26.1 (CH_2), 24.9 (CH_2), 24.0 (CH_2), 21.9 (CH_3), 21.4 (CH_3), 17.2 (CH_3), 17.1 (CH_3), 16.7 (CH_3). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{51}O_5^+$ $[M + H]^+$ 527.3737, found 527.3736.

General Procedure for Reaction via Pathway d. A flame-dried (under vacuum) round-bottom flask was cooled to −78 °C and charged with $BF_3{\cdot}Et_2O$ (purified, redistilled) (10 equiv) followed by the addition of DCM (0.14 M in starting material) The solution of aldol adduct (1 equiv) in DCM (0.14 M in starting material) was then added dropwise to the reaction mixture at −78 °C, allowed to warm to rt overnight, and stirred at this temperature for a total of 18 h, at which time the solvent was removed under vacuum, water (2 mL) was added to the solution, the 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.

*Reaction of **8** via Pathway d.* Following the general procedure for reaction via pathway d, the use of **8** (75 mg, 0.1377 mmol), $BF_3{\cdot}Et_2O$ (195.4 mg, 1.377 mmol, 173 μL), and DCM (2 mL) gave, after column chromatography, **12** (67 mg, 92%): R_f = 0.58 (EA/hex = 3/7).

*Reaction of **10** via Pathway d.* Following the general procedure for reaction via pathway d, the use of **10** (37 mg, 0.068 mmol), $BF_3{\cdot}Et_2O$ (96.5 mg, 0.68 mmol, 85 μL), and DCM (1.4 mL) gave, after column chromatography, **13** (19 mg, 53%), R_f = 0.5 (EA/hex =25/75), and **14** (8 mg, 22%), R_f = 0.43 (EA/hex =25/75).

(2*R*,4a*S*,6a*S*,7a*S*,8a*S*,10*S*,12a*S*,13a*S*,14a*S*,14b*R*)-Methyl 10-Acetoxy-7a-hydroxy-2,4a,6a,9,9,12a,14a-heptamethyl-7,13-dioxodocosahydrobenzo[*a*]tetracene-2-carboxylate (15). A round-bottom flask open to atmosphere was charged with basic alumina (11 g, 107.4 mmol), followed by the addition of DCM (5.7 mL). A solution of **6** (600 mg, 1.074 mmol) in DCM (5 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 24 h, at which time the mixture was filtered on a fine sinter funnel and washed successively with ethyl acetate. After the removal of the solvent in vacuo, column chromatography on silica yielded **15** as white solid (480 mg, 80%). Mp: 292 °C. R_f = 0.37 (EA/hex =3/7). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.52 (m, 1H), 3.59 (s, 3H), 2.90 (m, 1H), 2.61(dd, J_1 = 16 Hz, J_2 = 8 Hz, 1H), 2.43 (m, 1H), 2.15 (m, 1H), 2.05 (s, 3H), 1.96 (ddd, J_1 = J_2 = 16 Hz, J_3 = 4 Hz, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.91 (s, 3H), 0.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 216.6 (CO), 213.8 (CO), 179.1 (CO), 171.0 (CO), 80.2 (CH), 75.5 (COH), 52.7 (C), 51.9 (CH_3), 47.3 (CH), 46.3 (C), 45.9 (CH), 43.8 (CH), 40.7 (C), 39.7 (C), 38.2 (C), 35.6 (CH_2), 35.4 (CH_2), 33.9 (CH_2), 32.7 (CH_3), 31.8 (CH_3), 30.9 (CH_2), 30.8 (C), 30.4 (CH_2), 29.9 (CH_2), 28.1 (CH_2), 27.7 (CH_3), 24.7 (CH_2), 23.8 (CH_2), 21.3 (CH_3), 21.0 (CH_3), 20.3 (CH_3), 19.8 (CH_3), 16.7 (CH_3). HRMS (EI): *m*/*z* calcd for $C_{33}H_{50}O_7$ $[M]^+$ 558.35565, found 558.35386.

Preparation of 16 and 17. A round-bottom flask open to atmosphere was charged with $RuCl_3$ (161 mg, 0.777 mmol) and $NaIO_4$ (1.66 g, 7.77 mmol), followed by the addition of H_2O (11.7 mL) and CH_3CN (7.8 mL). To the resulting dark suspension was added a solution of **7** (420 mg, 0.777 mmol) in CCl_4 (7.8 mL) by a quick syringe transfer. The flask was sealed with a glass stopper, and the resulting biphasic mixture was vigorously stirred for 7 days, at which time 5 mL of ethanol was added to the solution. Subsequently, layers were separated and 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 flash column chromatography with gradient elution to give **16** as a yellow solid (75 mg, 18%). Mp: 186−188 °C. R_f = 0.76 (EA/hex =1/1); unreacted **7** (18 mg), R_f = 0.76 (EA/hex =1/1). Compound **19** was obtained as a transparent oil (26 mg, 6%): R_f = 0.56 (EA/hex =1/1). Compound **17** was obtained as a yellow solid (92 mg, 21%). Mp: 93−96 °C. R_f = 0.1 (EA/hex = 1/1).

(2*R*,4a*S*,6a*S*,9a*S*,11*S*,13a*S*,16a*S*,16b*R*)-Methyl 11-Acetoxy-2,4a,6a,10,10,13a,16a-heptamethyl-7,8,14,15-tetraoxodocosahydrobenzo[6,7]cyclodeca[1,2-*a*]naphthalene-2-carboxylate (16). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.74 (dd, J_1 =12 Hz, J_2 = 3.6 Hz, 1H), 3.74 (s, 3H), 3.51 (d, J = 13.2 Hz, 1H), 3.28 (dd, J_1 =14.4 Hz, J_2 = 4.2 Hz, 1H), 2.76 (ddd, J_1 = J_2 = 13.8 Hz, J_3 = 3.6 Hz, 1H), 2.59 (dd, J_1 = 10.2 Hz, J_2 = 3.6 Hz, 1H), 2.34 (d, J = 16.2 Hz, 1H), 2.28 (d, J = 14.4 Hz, 1H), 2.07 (s, 3H), 1.48 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 207.4 (CO), 205.9 (CO), 203.6 (CO), 201.1 (CO), 178.7 (CO), 170.6 (CO), 79.1 (CH), 53.3 (C), 52.1 (CH_3), 51.1 (C), 45.8 (CH), 44.0 (C), 42.5 (CH_2), 41.6 (CH), 40.6 (C), 38.7 (C), 38.5 (CH_2), 35.1 (CH_2), 34.7 (CH_2), 33.7 (CH_2), 32.7 (CH_3), 32.0 (C), 31.6 (CH_2), 31.4 (CH_3), 29.69 (CH_2), 29.67 (CH_2), 27.7 (CH_3), 23.4 (CH_2), 21.4 (CH_3), 18.0 (CH_3), 17.4 (CH_3), 17.2 (CH_3), 16.5 (CH_3). HRMS (ESI): *m*/*z* calcd for $C_{33}H_{48}O_8Na^+$ $[M + Na]^+$ 595.3247, found 595.3256.

(1*S*,2*S*,4a*R*,7*R*,8a*R*)-1-(3-((1*S*,2*S*,4*S*)-4-Acetoxy-2-(carboxymethyl)-1,3,3-trimethylcyclohexyl)-2,3-dioxopropyl)-7-(methoxycarbonyl)-1,2,4a,7-tetramethyldecahydronaphthalene-2-carboxylic Acid (17). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 9.65 (br s), 4.73 (dd, J_1 =11.4 Hz, J_2 = 4.2 Hz, 1H), 3.62 (s, 3H), 3.52 (d, J = 19.8 Hz, 1H), 2.80 (dd, J_1 = J_2 = 4.8 Hz, 1H), 2.64 (d, J = 19.8 Hz, 1H), 2.47 (dd, J_1 =17.4 Hz, J_2 = 5.4 Hz, 1H), 2.18 (dd, J_1 =17.4 Hz, J_2 = 5.4 Hz, 1H), 2.07 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 204.6 (CO), 199.7 (CO), 183.9 (CO), 179.5 (CO), 179.5 (CO), 170.8 (CO), 79.1 (CH), 51.8 (CH_3), 50.4 (C), 47.2 (C, br), 45.8 (CH_2, br), 43.6 (CH), 42.9 (C, br), 42.6 (C, br), 40.4 (CH, br), 38.9 (C), 37.9 (CH_2, br), 33.7 (C), 32.9 (CH_2, br), 32.4 (CH_2), 32.2 (CH_2, br), 30.5 (CH_3), 29.8 (CH_2, br), 29.4 (CH_2), 28.6 (CH_2, br), 27.7 (CH_3), 24.5 (CH_3, br), 23.1 (CH_2), 22.7 (CH_3, br), 21.4 (CH_3),

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20.5 (CH_3, br), 17.6 (CH_3, br), 17.3 (CH_3, br). HRMS (ESI): m/z calcd for $C_{33}H_{50}O_{10}Na^+$ $[M + Na]^+$ 629.3301, found 629.3299.

(1*S*,2*S*,4a*R*,7*R*,8a*R*)-Dimethyl 1-(3-((1*S*,2*S*,4*S*)-4-Acetoxy-2-(2-methoxy-2-oxoethyl)-1,3,3-trimethylcyclohexyl)-2,3-dioxopropyl)-1,2,4a,7-tetramethyldecahydronaphthalene-2,7-dicarboxylate (18). Solution of **17** (30 mg, 0.05 mmol) in diethyl ether (1 mL) in a round-bottomed flask was cooled to 0 °C, followed by a dropwise addition of solution of diazomethane in ether (about 2 mL total), and the reaction mixture was stirred at 0 °C until full conversion of the starting material was detected by TLC (approximately 15 min). The excess of diazomethane was quenched by a drop of glacial acetic acid, the solvent was removed in vacuo, and the crude product was further purified by column chromatography on silica to give trimethyl ester **18** as a white solid (29.5 mg, 93%). Mp: 114−117 °C. R_f = 0.7 (EA/hex =1/1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.69 (dd, J_1 = 11.6 Hz, J_2 = 4 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.62 (s, 3H), 3.51 (d, J = 20 Hz, 1H), 2.77 (dd, J_1 = 6.4 Hz, J_2 = 5.2 Hz, 1H), 2.72 (d, J = 20 Hz, 1H), 2.44−2.31 (3H), 2.06 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 1.20 (s, 3H), 1.08 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 205.5, 200.9, 179.5, 177.9, 174.0, 170.7, 79.1, 52.0, 46.9, 46.1, 44.2, 43.0, 42.6, 40.1, 38.8, 38.2, 33.7, 33.6 (br), 32.4, 31.9, 30.7, 30.0, 29.5, 28.4 (br), 27.7, 24.4, 23.1, 23.0, 21.4, 19.9 (br), 17.31 (br), 17.28 (br). HRMS (EI): m/z calcd for $C_{35}H_{54}O_{10}^+$ $[M]^+$ 634.37170, found 634.36992.

Preparation of 19 and 20. A solution of diisopropylamine (10.7 mg, 0.1056 mmol, 15 μL) in dry THF (2 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, 0.1056 mmol, 42 μL). The reaction mixture was warmed to 0 °C, stirred at this temperature for 5 min, and then cooled to −78 °C. A solution of **16** (55 mg, 0.096 mmol) in dry THF (3 mL) was then added dropwise to the solution of LDA by syringe at −78 °C. The reaction mixture was stirred at this temperature for 30 min, at which time the reaction was quenched by H_2O (D_2O) (2 mL). Following the addition of DCM (2 mL), the layers were separated, and the aqueous layer was extracted with DCM. The organic fractions were combined, washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave crude product mixtures that were further separated by chromatography. Column chromatography on silica yielded an inseparable mixture of compounds (7 mg) containing **20**, R_f = 0.43 (EA/hex = 4/6), and pure **19** as a transparent oil (36 mg, 64%), R_f = 0.31 (EA/hex = 4/6). A mixture of unidentifiable compounds containing **20** was further purified by semiprep HPLC (Agilent C18 column 21.2 × 250 mm, isocratic elution CH_3CN/H_2O = 8/2, flow rate 5 mL/min) to yield **20** as a white foam (5 mg, 9%). t_R = 30 min.

(2*R*,4a*S*,6a*S*,8*S*,9a*S*,11*S*,13a*S*,14*R*,16a*S*,16b*R*)-Methyl 11-Acetoxy-8,14-dihydroxy-2,4a,6a,10,10,13a,16a-heptamethyl-7,15-dioxodocosahydro-8,14-epoxybenzo[6,7]cyclodeca[1,2-*a*]-naphthalene-2-carboxylate (19, 6-H). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.65 (dd, J_1 =11.4 Hz, J_2 = 3.6 Hz, 1H), 3.74 (s, 3H), 3.14 (d, J = 12 Hz, 1H), 3.08 (br s, 1H), 2.91 (br S, 1H), 2.75 (2H), 2.37 (d, J = 15.6 Hz, 1H), 2.31−2.23 (2H), 2.18 (d, J = 12 Hz, 1H), 2.05 (s, 3H), 1.82 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.71 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 207.6 (CO), 205.1 (CO), 178.6 (CO), 170.9 (CO), 100.9 (COH), 99.0 (COH), 79.9 (CH), 55.0 (C), 52.1 (CH_3), 44.8 (CH), 44.6 (C), 43.6 (CH_2), 40.6 (C), 40.5 (CH), 40.1 (C), 37.3 (C), 35.8 (CH_2), 34.7 (CH_2), 32.7 (CH_3), 31.6 (CH_2), 31.54 (CH_3), 31.47 (C), 29.8 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 27.8 (CH_3), 23.6 (CH_2), 21.4 (CH_3), 16.92 (CH_3), 16.88 (CH_3), 16.5 (CH_3), 16.0 (CH_3). HRMS (ESI): m/z calcd for $C_{33}H_{50}O_9Na^+$ $[M + Na]^+$ 613.3353, found 613.3352.

Hemiketal (19, 6-D). ^{2}H NMR (600 MHz, $CHCl_3$, δ): 1.35 (br m). HRMS (ESI): m/z calcd for $C_{33}H_{49}DO_9Na^+$ $[M + Na]^+$ 614.34098, found 614.34077.

(2*R*,4a*S*,6a*S*,8a*R*,8b*S*,10*S*,12a*S*,13a*S*,14a*S*,14b*R*)-Methyl 10-Acetoxy-13a-hydroxy-2,4a,6a,9,9,12a,14a-heptamethyl-7,8,13-trioxodocosahydrobenzo[*a*]naphtho[1,2-*f*]azulene-2-carboxylate (20). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.49 (dd, J_1 = 12 Hz, J_2 = 4.8 Hz, 1H), 3.62 (s, 3H), 3.40 (d, J = 13.8 Hz, 1H), 2.76 (d, J = 15 Hz, 1H), 2.58 (d, J = 16.2 Hz, 1H), 2.22 (d, J = 13.8 Hz, 1H), 2.06 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.51 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 216.1 (CO), 209.9 (CO), 209.7 (CO), 178.9 (CO), 170.8 (CO), 80.0 (CH), 78.9 (COH), 57.6 (CH), 54.2 (C), 52.1 (CH_3), 50.0 (CH), 47.3 (C), 44.5 (CH), 43.6 (CH_2), 40.6 (C), 40.0 (C), 39.9 (C), 35.7 (CH_2), 33.9 (CH_2), 32.5 (CH_3), 32.1 (C), 31.52 (CH_2), 31.45 (CH_3), 30.9 (CH_2), 29.8 (CH_2), 27.3 (CH_3), 23.8 (CH_2), 23.7 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 18.0 (CH_3), 17.8 (CH_3). HRMS (EI): m/z calcd for $C_{33}H_{48}O_8^+$ $[M]^+$ 572.33492, found 572.33395.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental methods, mechanistic considerations for the formation of **10** and **11**, conformational analysis of **4**, **6**, **16**; complete ref 46; ^{1}H and ^{13}C NMR spectra of all new compounds, as well as HMQC, HMBC, COSY, and NOESY NMR spectra and the key COSY, HMBC, and NOESY correlations of compounds **6**, **8**−**10**, **12**−**15**, **17**, **19**, and **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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