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Formal Syntheses of (±)-Platensimycin and (±)-Platencin via a Dual-Mode Lewis Acid Induced Cascade Cyclization Approach

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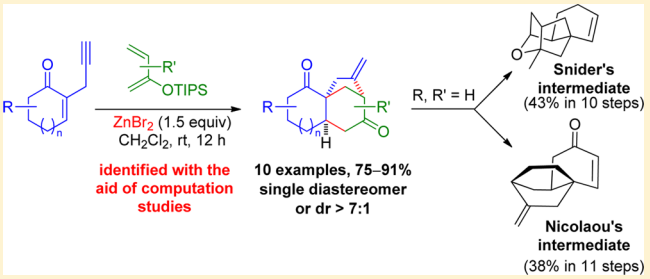
Supporting Information

ABSTRACT: A mild and efficient dual-mode Lewis acid induced Diels–Alder (DA)/carbocyclization cascade cyclization reaction has been developed for construction of the tricyclic core of *ent*-kaurenoids in one pot with the aid of a theoretical study on the π,σ-Lewis acidities of a variety of Lewis acids. With $ZnBr_2$ as the dual-mode Lewis acid, a series of substituted enones and dienes underwent DA/carbocyclization cascade cyclization reaction smoothly at room temperature and provided the tricyclic cyclized products in one pot with good yields and high diastereoselectivity. The tricyclic cyclized product has been successfully utilized as a common intermediate for formal syntheses of (±)-platensimycin and (±)-platencin.



INTRODUCTION

Platensimycin (**1**)[1] and platencin (**2**)[2] are potent bacterial type-II fatty acid biosynthesis inhibitors, which were isolated from *Streptomyces patensis* MA 7327 and 7339 by a research group at Merck & Co., Inc. in 2006 and 2007, respectively. Both platensimycin and platencin bear the same 3-amino-2,4-dihydroxybenzoic acid side chain with a different cage structure (an oxatetracyclic structure for platensimycin and a tricyclic carbocycle for platencin) (Figure 1). A recent study suggested that the biosynthesis of **1** involved an *ent*-kaurene-type intermediate that was derived from *ent*-copalyl pyrophosphate (CPP).[3,4] Platensimycin is a potent and selective inhibitor of FabF (the enzyme that catalyzed the elongation step in bacterial fatty acid synthesis),[1] while platencin is a moderate inhibitor of both FabF and FabH (the enzyme that catalyzed the initial condensation step in bacterial fatty acid synthesis).[2] With their unique mode of biological actions, these natural products showed potent antibacterial activities against a broad spectrum of multi-drug-resistant Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) with no observed toxicity.[5−9] However, the development of **1** and **2** into promising drug candidates has been greatly limited by their poor in vivo efficacy and pharmacokinetic properties.[10] As such, a tremendous amount of effort[11−18] has been invested in the synthesis of platensimycin[19−51] and platencin[52−72] as well as their structural analogues. Up to now, only a very limited number of platensimycin and platencin analogues have been reported to be more potent than the parent natural products,[43] and the development of structural analogues of platensimycin and platencin with improved in vivo efficacy and pharmacokinetic properties remains a challenge. Therefore, developing an efficient and versatile synthetic entry to platensimycin and platencin analogues is important for facilitating the develop-

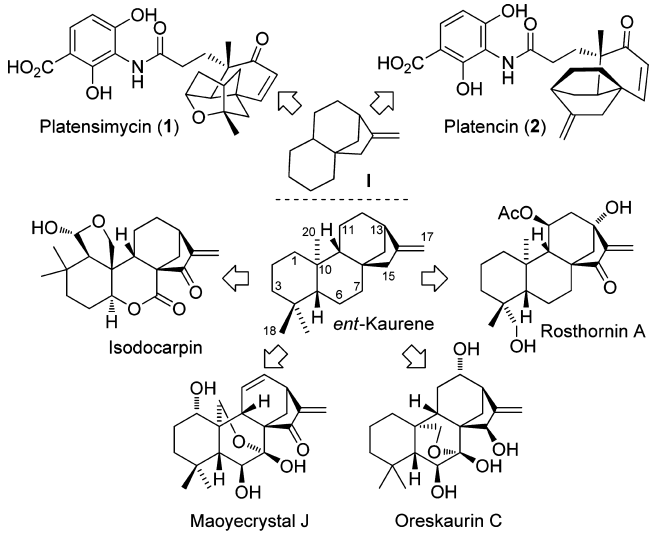


Figure 1. Tricyclic core of *ent*-kaurenoids (**I**) and examples of *ent*-kaurene related natural products.

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ment of these natural products into promising leads in drug discovery.

Dual-mode Lewis acids[73−77] are useful for developing cascade cyclization reactions since they can induce cyclization reactions via forming σ- and/or π-complexes with the substrates as well as the intermediate(s) that are generated in situ. We are particularly interested in developing dual-mode Lewis acid induced cascade cyclization reactions for natural product syntheses since they can often construct the core structure of the synthetic target in a single operation under mild conditions.[78−83] Recently, we have developed the $ZnBr_2$-catalyzed Diels−Alder (DA)/carbocyclization cascade cyclization reaction for the rapid construction of *cis*-hydrindanes and demonstrated its utilities in natural product synthesis.[80] As such, we have decided to employ this strategy for developing a new cascade cyclization reaction that could give a rapid access to the tricyclic fused ring system **I** (Figure 1), which is an important structural motif of the *ent*-kaurene related natural products[84−86] and is anticipated to provide rapid access to the cage structures of platensimycin (**1**) and platencin (**2**).

As shown in Figure 2, our strategy involved a Lewis acid induced DA cycloaddition of enone **3a** with diene **4a**. The

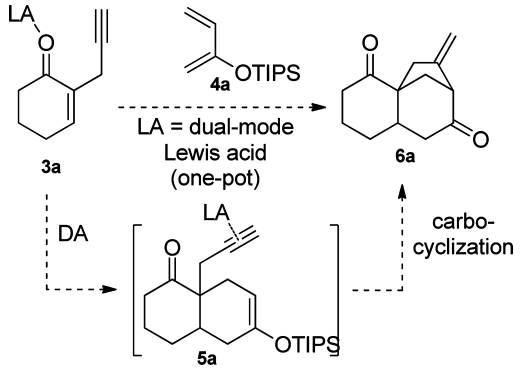

Figure 2. Rapid access to the 6,6,5-tricyclic fused ring system via the dual-mode Lewis acid induced cascade cyclization approach.

resulting silyl enol ether of the DA adduct **5a** could undergo intramolecular carbocyclization with the alkyne to form the bicycle[3.2.1]octane moiety of **6a** in a one-pot manner. This strategy requires a mild dual-mode Lewis acid that can form σ-complexes with enone **3a** for inducing the DA cycloaddition and π-complexes with intermediate **5a** for inducing the carbocyclization without causing hydrolysis of silyl enol ethers **4a** and **5a**. We have previously reported the dual-mode Lewis acid induced DA/carbocyclization cascade cyclization reaction for construction of the 6,6,5-tricyclic cyclized product **6a** and its application in the formal synthesis of platensimycin (**1**).[83] We herein report the computational and experimental details on the method development and demonstrate the utilities of the cascade reaction by employing the cyclized product (**6a**) as a common building block for the formal syntheses of (±)-platensimycin (**1**) and (±)-platencin (**2**).

RESULTS AND DISCUSSION

Theoretical Investigation of the Binding Enthalpies of Lewis Acids toward σ- and π-Electrons. In search of a suitable dual-mode Lewis acid for developing the DA/carbocyclization cascade cyclization reaction, the binding enthalpies between a variety of Lewis acids and the π/σ-complex partners, including propene/acetaldehyde (Table 1) and styrene/benzaldehyde (Table S1 in Supporting Information), were evaluated by density functional theory (DFT) calculations. As shown in Table 1 and Table S1, only slight differences in binding enthalpies were found between the alkyl and aryl compounds. In general, Lewis acids based on the main-group elements, such as MgX_2 and AlX_3, have stronger σ-binding than π-binding. On the other hand, the π-binding enthalpies of the transition-metal-based Lewis acids, such as AuCl and $Pd(OAc)_2$, are higher, owing to the π-back-bonding from the d-electrons of the transition metal to π^* orbital of substrates. These results are consistent with a similar theoretical study on the B3LYP/SDD values of a smaller set of Lewis acids reported by Yamamoto.[75]

To induce the DA/carbocyclization cascade cyclization reaction, the π/σ-binding energies of the Lewis acid should be high enough to promote sequential cyclization reactions. To identify the appropriate Lewis acid for the cascade reaction, the π-binding enthalpies (ΔH_π) were plotted against the differences of π/σ-binding enthalpies ($\Delta H_\pi - \Delta H_\sigma$). As shown in Figure 3, Zn(II)-, In(III)-, and Fe(III)-based Lewis acids have similar properties (within the box in Figure 3) with π-binding enthalpies of −10 to −30 kcal mol^{-1} and σ/π-binding enthalpy differences ($\Delta H_\pi - \Delta H_\sigma$) of −2 to −7 kcal mol^{-1}. More importantly, we have previously demonstrated that In(III) and Zn(II) are effective dual-mode Lewis acids for inducing the Prins/Conia-ene[78,81] and Michael/Conia-ene[79,82] cascade cyclization reactions, respectively. Taking these results into consideration, we identified a subgroup of Lewis acids that are promising for the development of the DA/carbocyclization cascade cyclization reaction.

Screening of Dual-Mode Lewis Acids. Based on the above analysis, the reaction between enone **3a** and diene **4a** was studied using a variety of In(III)-, Zn(II)-, and Fe(III)-based Lewis acids. As shown in Table 2, $InCl_3$ in acetonitrile led to an 80% yield of side product **7**, which could be formed via hydration of the alkyne moiety of **3a** even under anhydrous conditions (Table 2, entry 1). However, employing the same condition for various protected but-3-yn-1-ols did not lead to any methyl ketone products (data not shown). These results indicated that the ketone moiety of **3a** could be cyclized with the In(III)-activated alkyne and form the cyclic enol ether intermediate (**9**-[**In**] in Figure 5), which could lead to the methyl ketone side product **7** upon hydrolysis. Switching the Lewis acid to $InBr_3$ resulted in only a trace amount of the expected cyclized product **6a** along with 60% of **7** (entry 2). $In(OTf)_3$ also gave side product **7** in 90% yield (Table 2, entry 3). Switching the solvent to dichloromethane resulted in rapid decomposition of the substrates (Table 2, entries 4−6).

The activities of a number of Zn(II)- and Fe(III)-based Lewis acids were then investigated. As shown in Table 3, no cyclization was observed when using Zn(II) triflate or halides in acetonitrile (Table 3, entries 1−4). $FeCl_3/CH_3CN$ resulted in the hydrolysis of **4a** (Table 3, entry 5). Switching the solvent to dichloromethane with Zn(II) triflate did not give any cyclized product (Table 3, entry 6), and the silyl enol ether diene (**4a**) was hydrolyzed slowly under these reaction conditions. Finally, we found that the cascade cyclization went smoothly by using Zn(II) halides in dichloromethane and afforded the tricyclic product **6a** bearing the *cis*-decalin efficiently and diastereoselectively (Table 3, entries 7−9). The reaction of **3a** and **4a** in the presence of $FeCl_3$ in CH_2Cl_2 led to about 40% of **6a** (Table 3, entry 10). Silyl enol ether **4a** was hydrolyzed rapidly under these conditions. The optimal reaction conditions are $ZnBr_2$

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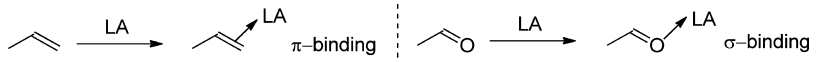
Table 1. Binding Enthalpies (in kcal mol^{-1}) of Lewis Acids toward Propene and Acetaldehyde and the Differences Calculated at M06/BSI[a]



Entry	LA			$\Delta H_\pi - \Delta H_\sigma$	Entry	LA			$\Delta H_\pi - \Delta H_\sigma$
1	AuCl	-41.9	-26.9	-15.0	16	$Zn(OTf)_2$	-24.4	-27.5	3.1
2	$Pd(OAc)_2$	-16.8	-3.2	-13.6	17	$ZnCl_2$	-20.5	-24.1	3.6
3	$AuCl_3$	-45.6	-33.9	-11.7	18	BF_3	-6.7	-11.5	4.8
4	CuCl	-37.8	-30.7	-7.1	19	BCl_3	-5.6	-11.4	5.8
5	AgCl	-27.3	-20.5	-6.8	20	$InBr_3$	-22.8	-28.6	5.8
6	AgOTf	-34.9	-28.4	-6.5	21	$InCl_3$	-23.1	-29.5	6.4
7	CuI	-33.7	-28.0	-5.7	22	$TiCl_4$	-5.9	-12.4	6.5
8	$CuCl_2$	-24.9	-21.7	-3.2	23	$In(OTf)_3$	-14.2	-20.8	6.6
9	$Ni(acac)_2$	-7.4	-5.2	-2.2	24	$SnCl_4$	-7.3	-15.4	8.1
10	$Cu(OAc)_2$	-10.3	-10.6	0.3	25	$MgBr_2$	-19.0	-28.2	9.2
11	$HgCl_2$	-13.1	-14.4	1.3	26	$MgCl_2$	-18.6	-28.0	9.4
12	$FeBr_3$	-28.9	-30.8	1.9	27	$AlMe_2Cl$	-12.8	-23.3	10.5
13	ZnI_2	-18.8	-21.3	2.5	28	$AlEt_2Cl$	-13.4	-24.2	10.8
14	$FeCl_3$	-29.3	-32.1	2.8	29	$AlCl_3$	-20.4	-31.8	11.4
15	$ZnBr_2$	-20.7	-23.8	3.1					

[a]See the Experimental Section for the computational methods.

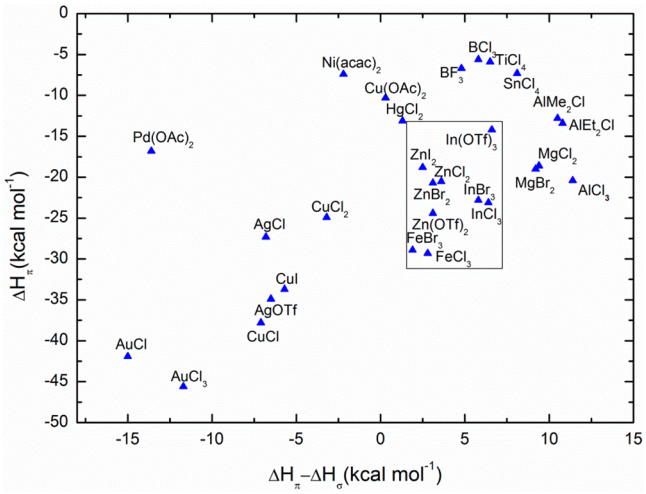
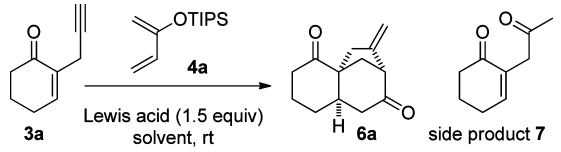


Figure 3. Plot of π-binding enthalpies (ΔH_π) versus the differences of π/σ-binding enthalpies ($\Delta H_\pi - \Delta H_\sigma$).

Table 2. In(III) as the Dual-Mode Lewis Acid for the Cascade Reaction[a]



entry	Lewis acid	solvent	yield[b] (**6a**)	yield[b] (7)
1	$InCl_3$	CH_3CN		80
2	$InBr_3$	CH_3CN	trace	60
3	$In(OTf)_3$	CH_3CN		90
4	$InCl_3$	CH_2Cl_2		
5	$InBr_3$	CH_2Cl_2		
6	$In(OTf)_3$	CH_2Cl_2		

[a]The general procedures were followed. [b]Isolated yields (%) after silica gel column chromatography.

(1.5 equiv) in CH_2Cl_2 at room temperature for 12 h. These mild conditions afforded the expected cyclized product **6a** in 86% yield as a single diastereomer (Table 3, entry 8), which was characterized unambiguously by NMR experiments[87] and X-ray crystallography.[88] Interestingly, $Zn(OTf)_2$/LiBr in CH_2Cl_2 also afforded good yields of cyclized product **6a** (Table 3, entry 11), suggesting that the addition of LiBr could facilitate the formation of a Zn(II) bromide dimer, which is presumably one of the active species under the reaction conditions.[89] However, $ZnBr_2$/LiBr gave only a trace amount of **6a** (Table 3, entry 12), hence the effect of LiBr is not clear in this situation. The extra LiBr might occupy the vacant site of the active species or promote the formation of unreactive metal halide clusters. A brief survey on the effects of solvents showed that $ZnBr_2$ in chloroform afforded a similar yield (Table 3, entry 13), but THF, 1,4-dioxane, toluene, or hexanes did not provide any cyclized product (Table 3, entries 14–17). The silyl enol ether diene **4a** was hydrolyzed slowly under these conditions. Reducing the loading of $ZnBr_2$ to 0.3 equiv led to an incomplete reaction and afforded only a 30% yield of **6a** (Table 3, entry 18). Increasing the reaction temperature resulted in a similar result (Table 3, entry 19).

Since Al(III)-based Lewis acids are known effective promoters for DA cycloadditions and are reported to be

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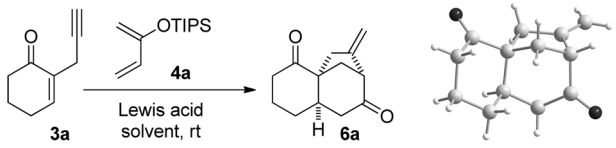
Table 3. Zn(II) and Fe(III) as the Dual-Mode Lewis Acid for the Cascade Reaction[a]

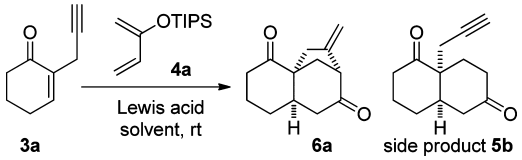


entry	Lewis acid	equiv	solvent	temp	yield[c]
1	$Zn(OTf)_2$	1.5	CH_3CN	rt	
2	$ZnCl_2$	1.5	CH_3CN	rt	
3	$ZnBr_2$	1.5	CH_3CN	rt	
4	ZnI_2	1.5	CH_3CN	rt	
5	$FeCl_3$	1.5	CH_3CN	rt	
6	$Zn(OTf)_2$	1.5	CH_2Cl_2	rt	
7	$ZnCl_2$	1.5	CH_2Cl_2	rt	74
8	$ZnBr_2$	1.5	CH_2Cl_2	rt	86
9	ZnI_2	1.5	CH_2Cl_2	rt	81
10	$FeCl_3$	1.5	CH_2Cl_2	rt	40
11	$Zn(OTf)_2/LiBr$[b]	1.5	CH_2Cl_2	rt	78
12	$ZnBr_2/LiBr$[b]	1.5	CH_2Cl_2	rt	trace
13	$ZnBr_2$	1.5	$CHCl_3$	rt	80
14	$ZnBr_2$	1.5	THF	rt	
15	$ZnBr_2$	1.5	1,4-dioxane	rt	
16	$ZnBr_2$	1.5	toluene	rt	
17	$ZnBr_2$	1.5	hexanes	rt	
18	$ZnBr_2$	0.3	CH_2Cl_2	rt	30
19	$ZnBr_2$	0.3	CH_2Cl_2	reflux	28

[a]The general procedures were followed. [b]One equivalent of LiBr was added. [c]Isolated yields (%) after silica gel column chromatography.

effective for carbocyclization with *endo*-selectivity,[90] a variety of Al(III) Lewis acids were studied. As shown in Table 4, no

Table 4. Al(III) as the Dual-Mode Lewis Acid for the Cascade Reaction[a]



entry	Lewis acid	solvent	temp	yield[b] (6a)	yield[b] (5b)
1	$EtAlCl_2$	CH_3CN	0 °C to rt		
2	$EtAlCl_2$	toluene	0 °C to rt		30
3	$EtAlCl_2$	CH_2Cl_2	0 °C to rt	trace	40
4	$Et_2AlCl/ZnBr_2$	CH_2Cl_2	−78 °C to rt	40	
5	$Me_2AlCl/ZnBr_2$	CH_2Cl_2	−78 °C to rt	76	

[a]The general procedures were followed. [b]Isolated yields (%) after silica column chromatography.

reaction was observed with $EtAlCl_2$ in acetonitrile, and the silyl enol ether was hydrolyzed under these conditions (Table 4, entry 1). Switching the solvent to toluene gave only the DA adduct **5a**, which was then hydrolyzed and gave modest yields of side product **5b** (Table 4, entry 2) after aqueous workup. Switching the solvent to CH_2Cl_2 provided only a trace amount of the 6,6,5-tricyclic product **6a** along with about 30−40% of side product **5b** after aqueous workup (Table 4, entry 3), while the potential 6,6,6-tricyclic product was not observed. Et_2AlCl or Me_2AlCl in CH_2Cl_2 followed by addition of $ZnBr_2$ afforded 40 and 60% yields of the 6,6,5-tricyclic product **6a**, respectively (Table 4, entries 4 and 5). These results indicated that Al(III) behaved more like an σ-Lewis acid in our system, which is consistent with the results of the above theoretical study.

Computational Investigation on the Mechanism of the Cascade Reaction. The mechanism of the DA/carbocyclization cascade cyclization reaction was studied by DFT calculations. The potential energy surfaces (PES) of the cascade reaction, with and without $ZnCl_2$, are shown in Figure 4. The free energy barrier of the DA reaction between unactivated **3a** and **4a** was calculated to be 32.1 kcal mol^{-1}, implying that the reaction is unlikely to take place at room temperature. In the presence of $ZnCl_2$, the free energy barrier for DA reaction is reduced to 25.4 kcal mol^{-1} (blue curve in Figure 4). $ZnCl_2$ activates **3a** through a σ-coordination to the carbonyl group. Following the rate-determining Diels−Alder reaction, **5a**-[**Zn**]-π,σ undergoes carbocyclization with a free energy barrier of 17.9 kcal mol^{-1}. Inspired by Yu's work,[89] we also considered the possibility of dimeric $[ZnCl_2]_2$ as a catalyst. Indeed, the reaction catalyzed by $[ZnCl_2]_2$ was calculated to be more favorable with an overall activation free energy of 22.2 kcal mol^{-1}. $[ZnCl_2]_2$ may bind to carbonyl and alkynyl with two Zn atoms, thus decreasing the strains. More importantly, dimeric $[ZnCl_2]_2$ stabilizes **8**-[**Zn**] by distributing the negative charges over the dimeric Zn moiety. The computational finding of the dimeric model could also account for the different reactivities of $Zn(OTf)_2$ and $Zn(OTf)_2$/LiBr (entries 6 and 11 in Table 3).

Comparison Study on the Effect of Different Lewis Acids. To understand the different reactivity of In(III)-, Al(III)-, and Zn(II)-based Lewis acids, further DFT calculations were conducted. The three potential energy surfaces of the reactions involving $InCl_3$, $AlMe_2Cl$, or $[ZnCl_2]_2$ are shown in Figure 5. The DA/carbocyclization cascade cyclization reaction is shown on the right side, while the competitive heterocyclization is shown on the left side. The results of the DFT calculations suggest different behaviors of these three Lewis acids. The $[ZnCl_2]_2$-catalyzed cascade reaction has been discussed above. Compared to the σ-complex **3a**-[**Zn**]-π,σ, the initial π-complex **3a**-[**Zn**]-π is less favorable by 7.3 kcal mol^{-1}. The relative free energy of the transition state for heterocyclization **HCy-TS**-[**Zn**] is lower than that of the DA reaction **DA-TS**-[**Zn**]. However, the following intermediate **9**-[**Zn**] is rather unstable, with a reaction free energy of 11.0 kcal mol^{-1} referring to **3a**-[**M**]. This implies that the cascade reaction is much more favorable thermodynamically.

For the case with $InCl_3$, both the activation free energy and reaction free energy for the heterocyclization are significantly lower than those of $ZnCl_2$. Combining the DFT results with the experimental observations, we propose that $InCl_3$ preferentially mediated the intramolecular heterocyclic reaction which would lead to the product **9**-[**In**] and then the side product **7** after hydrolysis. The $AlMe_2Cl$-mediated heterocyclization, however, is highly unfavorable (similar to that of $ZnCl_2$). Furthermore, the weak Al−π interaction cannot activate the carbocyclization process both kinetically and thermodynamically. The free energy barrier is 9.1 kcal mol^{-1} higher than that of the $ZnCl_2$-catalyzed process, and the intermediate is 12.0 kcal mol^{-1} higher in free energy than the DA intermediate, implying that the reaction catalyzed by $AlMe_2Cl$ is likely to stop at the first step. This is consistent with the experimental results.

Based on this theoretical study, $InCl_3$ is a better π-Lewis acid that activates the triple bond to promote the intramolecular

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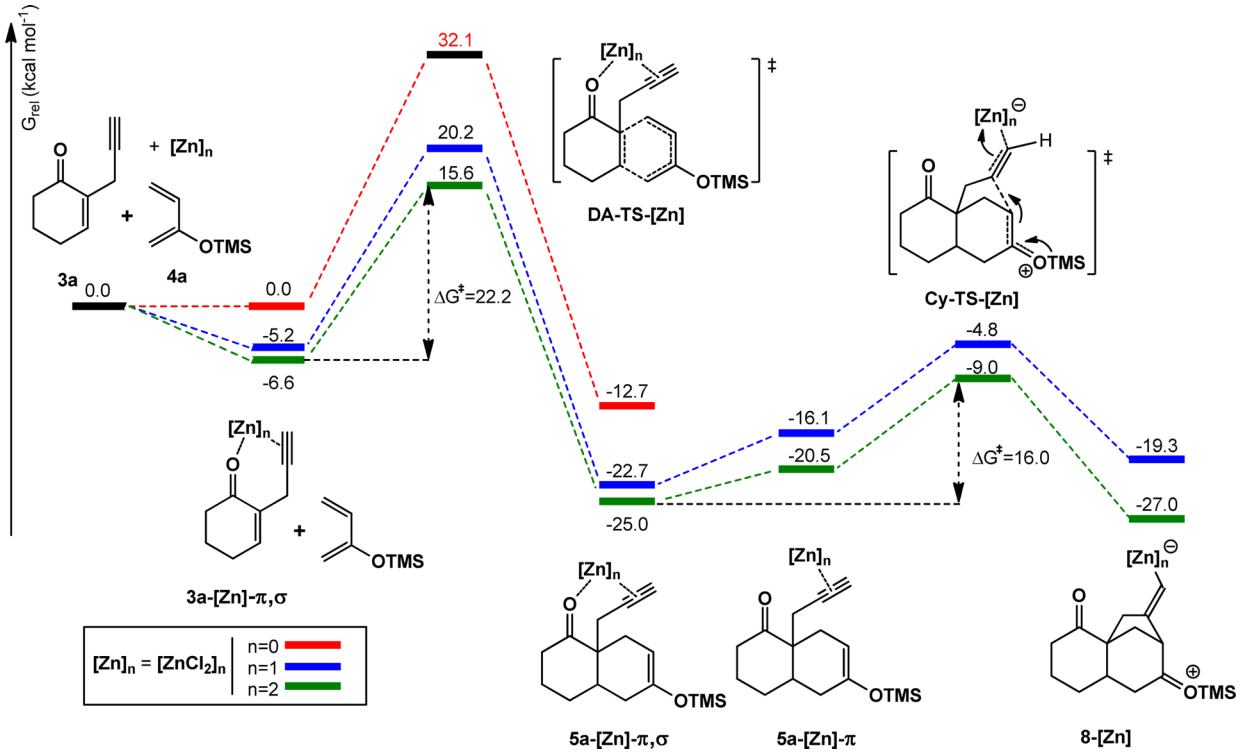

Figure 4. Potential energy surfaces of the cascade cyclization reaction of enone with diene in the absence (red lines) and presence of $ZnCl_2$ (blue line) or $(ZnCl_2)_2$ (green line) calculated at M06/BSII//M06/BSI. Relative free energies at 298 K are given in kcal mol^{-1}.

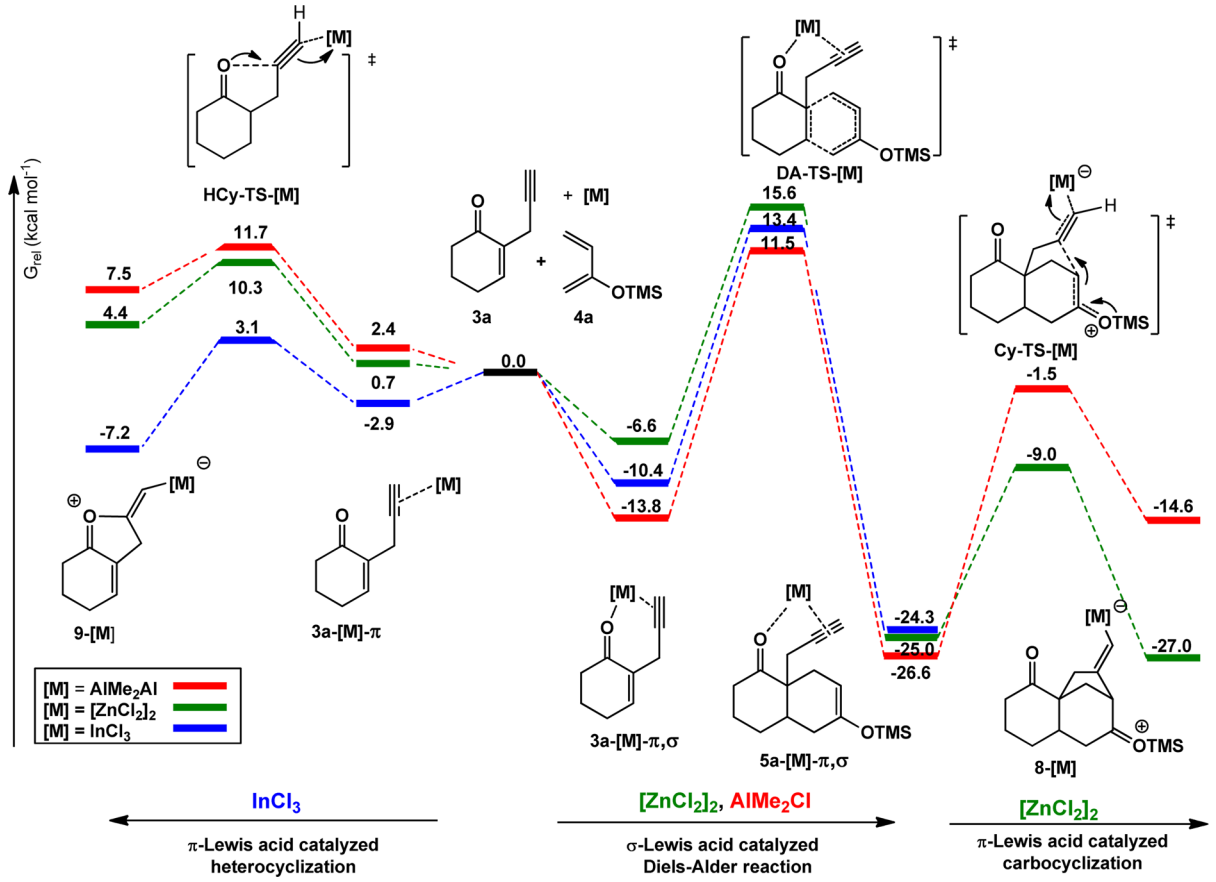

Figure 5. Potential energy surfaces computed for the reaction of enone with diene catalyzed by $AlMe_2Cl$ (red), $[ZnCl_2]_2$ (green), or $InCl_3$ (blue) calculated at M06/BSII//M06/BSI. Relative free energies at 298 K are given in kcal mol^{-1}.

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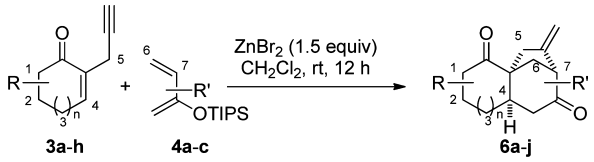
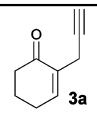
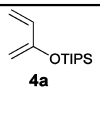
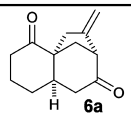
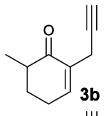
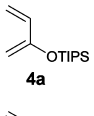
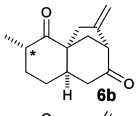
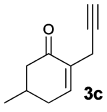
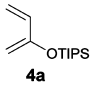
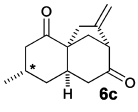
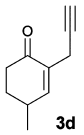
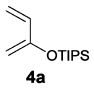
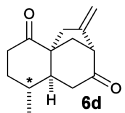
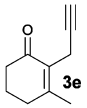
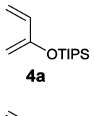
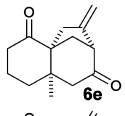
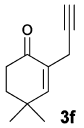
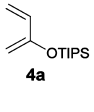
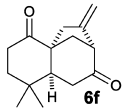
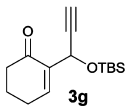
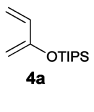
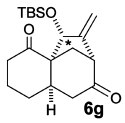
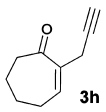
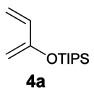
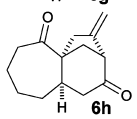
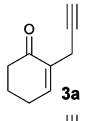
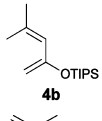
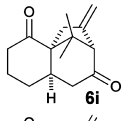
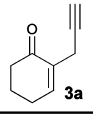
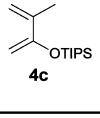
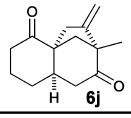
heterocyclic reactions of the enone. $AlMe_2Cl$ is a better σ-Lewis acid that can only promote the DA reaction by coordinating to the carbonyl as a σ-Lewis acid, whereas $ZnCl_2$ is a dual-mode Lewis acid that efficiently induces the cascade cyclization reaction, acting both as a σ- and then as a π-Lewis acid.

Study on the Scope of Substrates. With the optimal conditions in hand, the scope of the substrates was studied with a series of substituted enones (**3a−h**) and dienes (**4a−c**). As shown in Table 5, methyl substituents at C1−C4 of the enone were well-tolerated and gave comparable yields and diastereoselectivity of the cyclized products (**6b−e**) (Table 5, entries 2−5). The diastereoselectivities of **6b,c** would be rationalized based on the preliminary conformational analysis in Figure 6. Addition of diene **4a** is expected from the face that is *anti* to the methyl substituent. More importantly, the geminal dimethyl substituent at C3 also afforded good yields of cyclized product **6f** (Table 5, entry 6). This result indicated that a quartenary carbon center adjacent to the reactive site can be tolerated under this cyclization condition. Introducing an OTBS moiety at C5 also afforded good yields and good diastereoselectivity (Table 5, entry 7). The observed diastereoselectivity of **6g** would be rationalized by a nonchelating Felkin-Anh model in Figure 6. The OTBS group preferentially orientates *anti* to the carbonyl for minimization of the dipole, and addition of diene **4a** is anticipated from the face that is *anti* to the OTBS group. These results indicate that these substituted enones and dienes not only afford comparable results but also provide a handle for developing asymmetric reactions via substrate control. Moreover, the seven-membered enone (**3h**) also gave good yields and good diastereoselectivity for the cyclized product **6h** (Table 5, entry 8), which could be a useful building block for the syntheses of grayanane-type diterpenes.[91] Diene **4b**, which bears two methyl substituents at the reactive site (C6) for the DA cycloaddition also reacted smoothly and gave the cyclized product (**6i**) as a single diastereomer (Table 5, entry 9).[88] The intermediate that arose from the double Michael reaction pathway was not observed under these reaction conditions. Diene **4c**, which bears a methyl group at C7 (the reactive site for the carbocyclization), also afforded a very good yield (91%) of the cyclized product (**6j**) diastereoselectively (Table 5, entry 10).

Table 5. Study on the Scope of Substrates[a]



Entry	Enones	Dienes	Product	Yields[b] (dr)
1	 **3a**	 **4a**	 **6a**	86[c]
2	 **3b**	 **4a**	 **6b**	81 (8:1)
3	 **3c**	 **4a**	 **6c**	88[c]
4	 **3d**	 **4a**	 **6d**	85 (16:1)
5	 **3e**	 **4a**	 **6e**	80[c]
6	 **3f**	 **4a**	 **6f**	80[c]
7	 **3g**	 **4a**	 **6g**	75 (7:1)
8	 **3h**	 **4a**	 **6h**	82[c]
9	 **3a**	 **4b**	 **6i**	79[c]
10	 **3a**	 **4c**	 **6j**	91[c]

[a]The general procedures were followed. [b]Isolated yields (%) after silica gel column chromatography. [c]A single diastereomer.

Applications in Natural Product Synthesis. To demonstrate the utility of this cascade cyclization reaction, the cyclized product **6a** was employed as a common precursor for the formal synthesis of platensimycin (**1**) and platencin (**2**). The retrosynthesis of **1** is shown in Scheme 1. The cage structure of the Snider's intermediate[21] (**10**) could be established via selective reduction of ketone **11**, followed by acid induced cationic cyclization. Ketone **11** could be obtained via 1,2-carbonyl migration of compound **12**, which could be prepared readily by differentiation of the two ketone moieties of **6a**. The retrosynthesis of **2** also employs **6a** as the starting material. As shown in Scheme 1, the bicyclo[2.2.2]octane moiety of Nicolaou's intermediate[52] (**13**) is expected to be established by radical rearrangement of **14**, which could be obtained from **15** via a 1,3-allylic rearrangement. Compound **15** could be also obtained from **6a** via differentiation of the ketone moieties.

Formal Synthesis of (±)-Platensimycin 1. Since both synthetic strategies involve the differentiation of two ketone moieties in **6a**, the conditions for direction reaction with the ketones were first investigated. Based on the preliminary conformational analysis of **6a**, the two ketone moieties should have significant differences in the steric hindrance that could be exploited for differentiation. However, treatment with 1 equiv of a bulky hydride, such as L, K-selectride or DIBAL, resulted in a roughly 3:1 mixture of **16a** and **16b** (Scheme 2) based on the NMR analysis of the crude product. Reduction of **6a** with $NaBH_4$ in a variety of conditions resulted in nonselective reduction. Reaction between **6a** and tosyl hydrazine resulted in a roughly 1:1 mixture of hydrazones (**17a** and **17b**) based on the NMR analysis of the crude product.

dx.doi.org/10.1021/jo401105q | J. Org. Chem. 2013, 78, 7912−7929

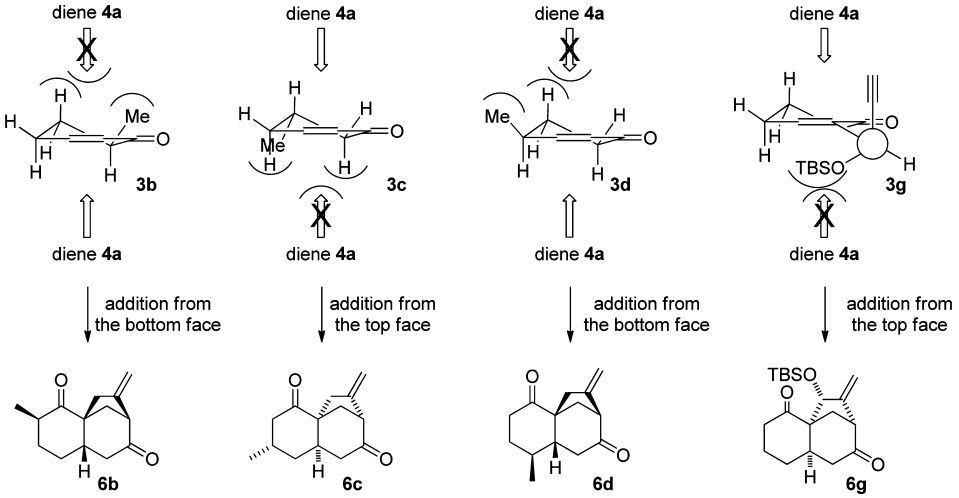
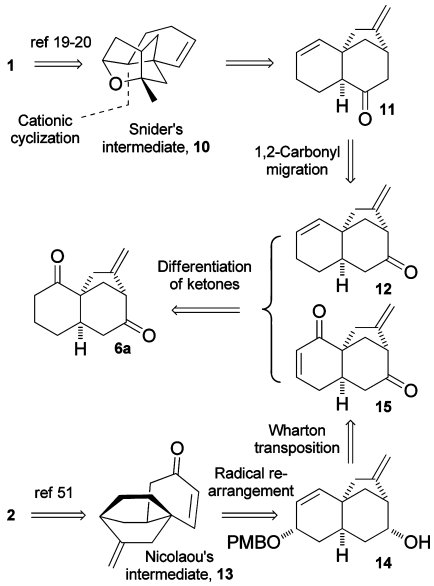
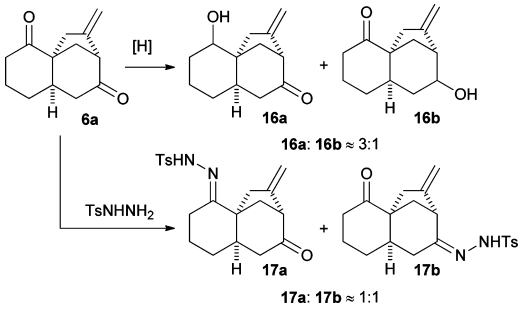


Figure 6. Rationale for the observed diastereoselectivity of **6b−d** and **6g**.

Scheme 1. Retrosynthetic Analysis of Platensimycin 1 and Platencin 2 from 6a

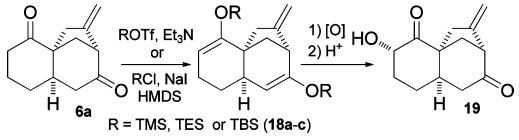


Scheme 2. Attempts at Ketone Differentiation of 6a



Diketone **6a** was thus converted to the silyl enol ethers (**18a−c**), which were epoxidized using a variety of oxidants. As shown in Table 6, epoxidation of **16a** with DMDO resulted in decomposition of the substrate (Table 6, entry 1). Switching the oxidant to *m*CPBA selectively afforded 10% of α-hydroxy ketone **19** as a single diastereomer along with about 20% of **6a** recovered (Table 6, entry 2). More bulky silyl enol ethers (**18b** and **18c**) led to an increase in yields to 30 and 60%, respectively (Table 6, entries 3 and 4). The yield of **19** was further optimized by using magnesium monoperoxyphthalate (MMPP), which provided **19** in 65−80% (Table 6, entries 5−7). The optimal yield was obtained from **18c** with MMPP as the oxidant at room temperature, which gave 80% yield of **19** with no hydrolysis of the silyl enol ethers being observed (Table 6, entry 7).

Table 6. Selective α-Hydroxylation of 6a[a]



entry	R	[O]	temp	yield[b]
1	TMS	DMDO	0 °C	
2	TMS	*m*CPBA	0 °C	10
3	TES	*m*CPBA	0 °C	30
4	TBS	*m*CPBA	0 °C	60
5	TMS	MMPP	0 °C	65
6	TES	MMPP	0 °C	75
7	TBS	MMPP	rt	80

[a]The crude intermediates (**18a−c**) were used without purification. [b]Isolated yields after silica gel column chromatography. MMPP = magnesium monoperoxyphthalate.

With **19** prepared, it was converted to ketone **12** via hydroxyl-directed reduction followed by elimination of the resulting diol (Scheme 3).[92,93] This protocol provided **10** in 75% yield. Silyl enol formation followed by MMPP epoxidation of **12** provided α-hydroxyl ketone **20** as a single diastereomer. However, acetylation of **20** under various acidic conditions resulted in a mixture of acetal isomers (**21a** and **21b**). After a survey of different acid conditions, we found that **20** can be equilibrated to **22** qualitatively and diastereoselectively with 2 N aqueous HCl overnight. Indeed, the α-hydroxylation of **22** with MMPP and equilibrium can be done conveniently in a one-pot manner, and the diastereomer bearing the *trans*-decalin was not observed under these reaction conditions. The resulting alcohol of **22** was then acetylated and deacetoxylated using SmI_2. Finally, reduction of ketone **11** with K-selectride followed by treatment of trifloroacetic acid[70] afforded the

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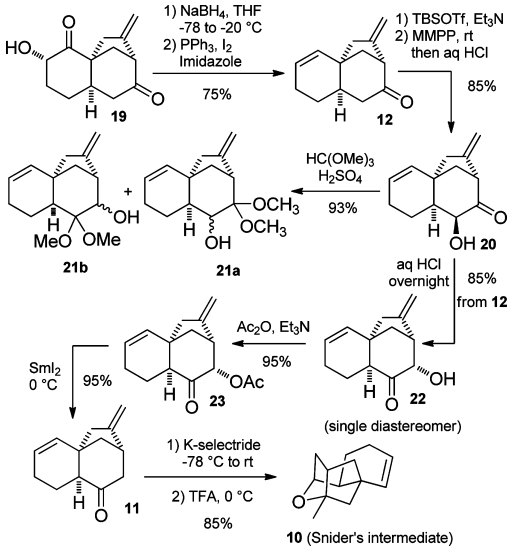
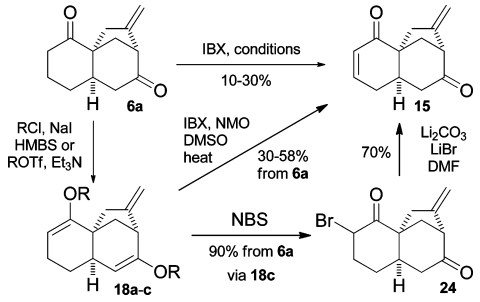
Scheme 3. Formal Synthesis of Platensimycin 1



Snider's intermediate[21] (**10**), which could be converted to **1** according to the literature procedures.[19,20]

Formal Synthesis of (±)-Platencin 2. For the formal synthesis of **2**, enone **15** was expected to be obtained via dehydration of α-hydroxyl ketone **19**. However, decomposition of **19** resulted under a variety of dehydration conditions. Preparation of enone **15** via oxidation of **6a** and **18a−c** was then examined. As shown in Scheme 4, oxidation of **6a** using

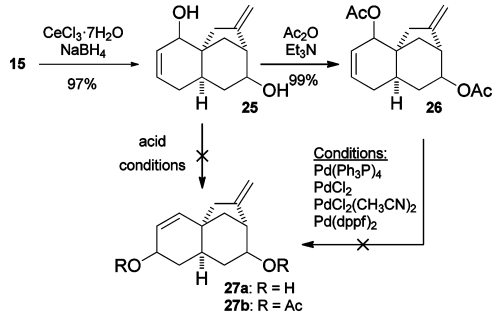
Scheme 4. Synthesis of Enone 15 via Selective Oxidation or Bromination



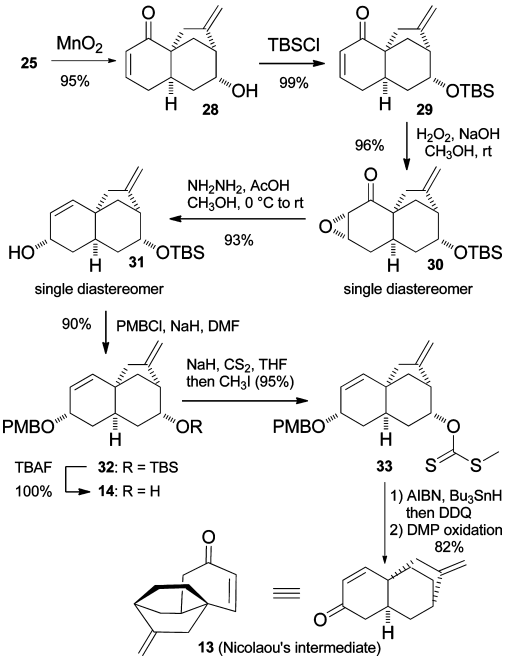
IBX provided 10−30% of the expected enone **13**. Switching the substrate to **18a−c** increased the yield of **15** up to 58% (from **18c**). Under these oxidation conditions, the reactions needed to be stopped before completion to avoid overoxidation. Finally, the yield of **15** was optimized via bromination of **18c**, followed by elimination.

With enone **15** in hand, the two ketones were reduced using Luche reduction[94] conditions (Scheme 5). The resulting diol **25** is a single diastereomer. Acetylation of **25** afforded diacetate **26** in good yield. The 1,3-allylic rearrangement of **25** and **26** was investigated with a variety of acids[95−97] and Pd catalysts,[98−102] respectively. However, these conditions resulted in either no reaction or decomposition of substrates. The allylic alcohol of **25** was thus selectively oxidized with MnO_2 (Scheme 6). After TBS protection of **28**, enone **29** was converted to **31** stereoselectively via the Wharton transposition protocol.[103] After a number of protecting and functional group manipulations, the bicycle[3.2.1]octane moiety was converted to the bicycle[2.2.2]octane using Yoshimitsu's procedures.[71] Finally,

Scheme 5. Study on the 1,3-Allylic Rearrangement



Scheme 6. Formal Synthesis of Platencin 2



oxidative removal of the PMB ether followed by oxidation of the resulting alcohol finished the synthesis of the Nicolaou's intermediate[52] (**13**), which can also be converted to **2** according to the literature procedures.[52]

Optimization of the Ketone Differentiation. The differentiation was further optimized by exhaustive reduction of the diketone with sodium borohydride (diol **34**, a roughly 3:1 diastereomeric mixture) followed by selective TBS protection, which afforded **35** in 78% yield as a roughly 3:1 diastereomeric mixture from **6a** (Scheme 7). The diastereomers are separable, and the stereochemistry of the major diastereomer of **35** was determined by NMR experiments.[87] Since the two newly generated stereogenic centers will be removed in the late stage of the synthesis, all the diastereomers can be used for the synthesis of **1** and **2**. Triflation of **35** followed by elimination afforded **37**. Finally, desilylation of **36** followed by oxidation of the resulting alcohol provided ketone **12**, which could lead to Snider's intermediate **10** in only seven steps. Oxidation of alcohol **35** followed by Saegusa oxidation[104] afforded enone **29**, which can lead to Nicolaou's intermediate **13** in 8 steps.

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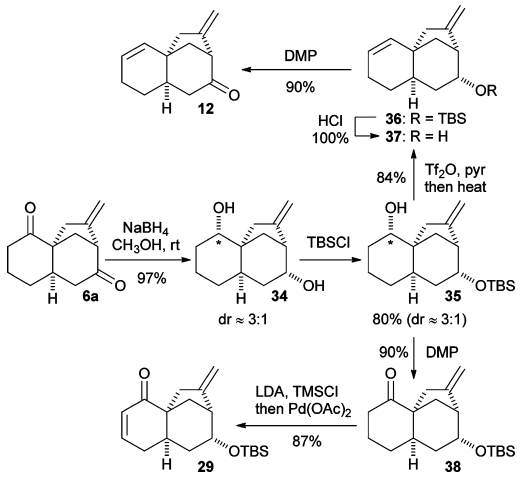
Scheme 7. Optimization of the Ketone Differentiation of 6a



CONCLUSION

In summary, we have evaluated the π/σ-binding properties of 29 commonly used Lewis acids in a theoretical study and successfully identified a subclass of Lewis acids, including In(III), Zn(II) and Fe(III) halides, with similar π/σ-binding properties. With the aid of these theoretical studies, we have developed a mild DA/carbocyclization cascade cyclization reaction with $ZnBr_2$ (1.5 equiv) as the dual-mode Lewis acid mediator, which rapidly provided the 6,6,5-tricyclic fused cyclized product **6a** from two simple substrates (**3a** and **4a**). The mechanism of this cascade reaction was further studied via a comparison study between In(III), Zn(II), and Al(III) induced reactions by DFT calculations. Under the optimal conditions ($ZnBr_2$ in CH_2Cl_2 at room temperature), a variety of substituted enones **3a**–**h** and dienes **4a**–**c** underwent cascade cyclization smoothly and afforded the cyclized products (**6a**–**j**) in one pot with good yields and high diastereoselectivity. The utility of this new cascade reaction has been successfully demonstrated by employing cyclized product **6a** as the common building block for the formal synthesis of (±)-platensimycin (**1**) and (±)-platencin (**2**) (43% in 10 steps and 38% in 11 steps overall yields from **6a**, respectively).

EXPERIMENTAL SECTION

General Computational Methods. All the calculations were carried out with the Gaussian 09 package.[105] Geometry optimizations and frequency calculations were performed with the M06 method[106−110] with BSI (the LANL2DZ basis set[111] and corresponding effective core potentials (ECPs)[112−114] for elements with atomic number higher than 36, and the 6-31G(d) basis set[115] for other atoms). The transition states (TS) were confirmed by frequency calculation and intrinsic reaction coordinate (IRC) calculations.[116−119] All the TS stationary points were correctly connected to the corresponding species. Vibrational frequency calculations also provide thermal corrections for enthalpies and Gibbs free energies (at 298.15 K and 1 atm). For reaction energy profile, single-point energies were calculated at the M06 level with a larger basis sets BSII (def2-TZVP[120−126] with ECP for In[127] and 6-311++G(3df,3pd) for other atoms). Solvent effects were taken into account by using the SMD solvation model.

General Experimental Methods. All air- and water-sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254) that were analyzed by fluorescence upon 254 nm irradiation or by staining with $KMnO_4$ (200 mL H_2O of 1.5 g of $KMnO_4$, 10 g of K_2CO_3, and 1.25 mL of 10% aqueous NaOH). Silica gel (60, particle size 0.0400.063 mm) was used for flash column chromatography. All the chemicals were purchased commercially and used without further purification. Anhydrous THF was distilled from sodium benzophenone. Toluene was distilled over Na. CH_3CN and CH_2Cl_2 were distilled from calcium hydride. Molecular sieves were activated by heating at 200 °C for 12 h at ∼1.0 Torr. Yields refer to the isolated yields after silica gel flash column chromatography, unless otherwise stated. NMR spectra were recorded on either a 300 (^{1}H, 300 MHz; ^{13}C, 75.5 MHz) or 500 MHz (^{1}H, 500 MHz; ^{13}C, 125.8 MHz) spectrometer. The NOESY experiments were performed on a 500 or 600 MHz spectrometer. The following abbreviations were used to explain themultiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra were obtained from a MALDI-TOF mass spectrometer. Melting points were uncorrected and determined on a micromelting point meter. Crystallographic data were obtained from a single-crystal X-ray diffractometer. All the IR spectra were recorded with a FTIR spectrometer.

*2-(Prop-2-yn-1-yl)cyclohex-2-enone (**3a**), 4,4-Dimethyl-2-(prop-2-yn-1-yl)cyclohex-2-enone (**3f**), and 2-(Prop-2-yn-1-yl)cyclohept-2-enone (**3h**).* To a stirred solution of NaOMe (prepared from sodium (1.25 g, 5.43 mmol) and CH_3OH (30 mL)) in methanol (50 mL) at 0 °C was added a solution of methyl thioglycolate (5.52 g, 5.21 mmol) in methanol (20 mL). After 5 min stirring at 0 °C, a solution of the appropriate enone (5.21 mmol) in methanol (20 mL) was added dropwise at the same temperature. The reaction mixture was allowed to warm to room temperature slowly and heated under reflux for 10 h. After removal of the volatiles, the resulting orange residue was dissolved in diethyl ether (50 mL) and extracted with a 2 N NaOH aqueous solution (30 mL × 2). The combined aqueous layer was acidified with a 1 N HCl aqueous solution (60 mL), extracted with diethyl ether (50 mL × 2), dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 10:1) afforded an orange-yellow liquid as the product. To a solution of this crude product in dry acetone (50 mL) were added powdered K_2CO_3 (3.6 g, 26.1 mmol) and 3-bromoprop-1-yne (2.5 g, 20.8 mmol). The reaction mixture was refluxed for 4 h. After TLC analysis showed the consumption of the starting material, the volatiles were removed in vacuo. The residue was poured onto ice/water and extracted with diethyl ether (100 mL × 2). The combined extracts dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in diethyl ether (50 mL), and a 5% NaOH aqueous solution (50 mL) was added. The reaction mixture was stirred for 4 h at room temperature. Then the organic layer was separated and washed with saturated $NaHCO_3$ solution followed by brine solution (50 mL × 2). After removal of the volatiles, the residue was purified by silica flash column chromatography (hexanes/ethyl acetate = 20:1). **3a** (a yellow oil, 35% in 3 steps from cyclohex-2-enone).[1] **3f** (a yellow oil, 32% in 3 steps from 4,4-dimethylcyclohex-2-enone): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 3.12 (t, J = 2.0 Hz, 2H), 2.50−2.46 (t, J = 6.8 Hz, 2H), 2.18 (t, J = 2.4 Hz, 1H), 1.85 (t, J = 6.80 Hz, 2H), 1.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 155.3, 130.9, 80.7, 71.8, 36.0, 34.3, 33.0, 27.8, 18.9; IR (neat, cm^{-1}) 2941, 2864, 1680, 1430, 1273, 1236, 1162, 876, 766; HRMS (ESI/[M + H]$^+$) calcd for $C_{11}H_{15}O$ 163.1123, found 163.1117. **3h** (a yellow oil, 32% in 3 steps from cyclohept-2-enone): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (tt, J = 6.4, 1.6 Hz, 1H), 3.19−3.17 (m, 2H), 2.62 (t, J = 6.12 Hz, 2H), 2.49−2.45 (m, 2H), 2.18 (t, J = 2.6 Hz, 1H), 1.80−1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 143.5, 137.4, 81.3, 71.7, 42.3, 27.4, 24.9, 21.6, 21.1; IR (neat, cm^{-1}) 2941, 2864, 1680, 1430, 1273, 1236, 1162, 876, 766; HRMS (ESI/[M + H]$^+$) calcd for $C_{10}H_{13}O$ 149.0966, found 149.0962.

*6-Methyl-2-(prop-2-yn-1-yl)cyclohex-2-enone (**3b**), 5-Methyl-2-(prop-2-yn-1-yl)cyclohex-2-enone (**3c**), 4-Methyl-2-(prop-2-yn-1-yl)-cyclohex-2-enone (**3d**), and 3-Methyl-2-(prop-2-yn-1-yl)cyclohex-2-enone (**3e**).* To a stirred solution of the appropriate β-keto ester (1 equiv) with the corresponding enal (or enone) (1 equiv) in tBuOH (1 M) was added a catalytic amount of tBuOK (0.05 equiv) at 0 °C. The mixture was stirred at that temperature for 30 min and then treated

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with 0.2 equiv of *t*BuOK. The resulting mixture was heated under reflux for 20 h. After cooling to room temperature, the reaction was quenched with a 1 N HCl aqueous solution (10 mL), diluted with diethyl ether (80 mL), and washed with a saturated $NaHCO_3$ aqueous solution (3 mL × 20) and brine (20 mL × 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexanes/ethyl acetate = 20:1). **3b** (a yellow liquid, 52% from ethyl 2-methyl-3-oxohept-6-ynoate and acrylaldehyde): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 1H), 3.15 (s, 1H), 2.48−2.38 (m, 3H), 2.17 (t, J = 2.6 Hz, 1H), 2.07 (qd, J = 12.8, 4.4 Hz, 1H), 1.75 (ddd, J = 25.6, 12.8, 7.6 Hz, 1H), 1.15 (d, J = 6.80 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.6, 145.2, 133.3, 81.0, 71.5, 41.6, 30.9, 25.2, 19.1, 15.0; IR (neat, cm^{-1}) 3299, 2942, 2874, 1660, 1431, 1362, 655; HRMS (ESI/[M + H]$^+$) calcd for $C_{10}H_{13}O$ 149.0966, found 149.0959. **3c** (a yellow liquid, 76% from ethyl 3-oxohept-6-ynoate and but-2-enal): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.13−7.12 (m, 1H), 3.14 (s, 2H), 2.54−2.46 (m, 2H), 2.23−2.07 (m, 4H), 1.05 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 145.3, 133.5, 80.7, 71.5, 46.0, 34.0, 30.3, 20.9, 18.7; IR (neat, cm^{-1}) 3295, 2948, 2874, 1663, 1431, 1365, 650; HRMS (ESI/[M + H]$^+$) calcd for $C_{10}H_{13}O$ 149.0966, found 149.0959. **3d** (a yellow liquid, 50% from ethyl 3-oxohept-6-ynoate and methacrylaldehyde): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 1.2 Hz, 1H), 3.18 (d, J = 1.6 Hz, 2H), 2.63−2.57 (m, 1H), 2.51 (td, J = 13.6, 3.6 Hz, 1H), 2.40−2.32 (m, 1H), 2.18 (t, J = 2.6 Hz, 1H), 2.15−2.03 (m, 1H), 1.76−1.59 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 151.7, 132.6, 80.7, 71.7, 36.8, 31.3, 30.9, 20.3, 18.8; IR (neat, cm^{-1}) 3293, 2942, 2871, 1670, 1427, 1380, 644; HRMS (ESI/[M + H]$^+$) calcd for $C_{10}H_{13}O$ 149.0966, found 149.0969. **3e** (a yellow liquid, 75% from ethyl 3-oxohept-6-ynoate and but-3-en-2-one): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (s, 2H), 2.43−2.37 (m, 4H), 2.05 (s, 3H), 1.98−1.92 (m, 2H), 1.89 (dd, J = 3.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 158.1, 130.8, 81.9, 67.2, 37.2, 32.8, 21.9, 21.4, 14.1; IR (neat, cm^{-1}) 3299, 2939, 1665, 1628, 1430, 1384, 1186, 649; HRMS (ESI/[M + H]$^+$) calcd for $C_{10}H_{13}O$ 149.0966, found 149.0976.

*2-(1-((tert-Butyldimethylsilyl)oxy)prop-2-yn-1-yl)cyclohex-2-enone (**3g**).* To a stirred mixture of 3-(trimethylsilyl)propiolaldehyde (4.5 g, 35.3 mmol), imidazole (3.0 g, 44.13 mmol), and TBAI (0.40 g, 1.06 mmol) in THF (35 mL) and a 1 N $NaHCO_3$ aqueous solution (140 mL) was added cyclohex-2-enone (6.8 mL, 70.6 mmol) at room temperature. The resulting mixture was stirred at room temperature for 48 h, then quenched with a 1 N HCl aqueous solution (100 mL), and extracted with CH_2Cl_2 (50 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 1:1) provided a colorless oil (4.02 g, 26.8 mmol, 76%) as the intermediate. 2-(1-Hydroxyprop-2-yn-1-yl)cyclohex-2-enone (**39**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, J = 4.0 Hz, 1H), 5.23 (s, 1H), 3.56 (d, J = 4.8 Hz, 1H), 2.57−2.56 (m, 1H), 2.48−2.42 (m, 4H), 2.03−1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 148.2, 137.3, 81.7, 74.8, 60.9, 38.2, 25.6, 22.3; IR (neat, cm^{-1}) 3480, 3307, 2920, 2857, 1682, 1070; HRMS (ESI/[M + H]$^+$) calcd for $C_9H_{11}O_2$ 151.0759, found 151.0768. To a stirred solution of **39** (1.44 g, 9.6 mmol) in CH_2Cl_2 (50 mL) were added imidazole (1.31 g, 19.2 mmol) and TBSCl (2.17 g, 14.4 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched with a saturated $NaHCO_3$ aqueous solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL × 3), and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 5:1) of the residue gave a yellow oil (2.49 g, 9.4 mmol, 98%) as the product. **3g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 2.8 Hz, 1H), 5.34 (s, 1H), 2.43−2.40 (m, 5H), 2.03−1.97 (m, 2H), 0.89 (s, 3H), 0.15 (s, 3H), 0.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 146.1, 139.1, 83.9, 72.5, 59.0, 38.3, 25.7, 25.7, 25.7, 22.6, 18.2, −3.6, −4.8, −5.2; IR (neat, cm^{-1}) 3305, 2957, 2920, 2870, 1680, 1470, 1378, 1260, 1067, 844, 771; HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{25}O_2Si$ 265.1624, found 265.1631.

General Procedures for the DA/Carbocyclization Cascade Cyclization Reactions. To a stirred solution of **3** (10 mmol) in CH_2Cl_2 (100 mL) was added the appropriate Lewis acid (15 mmol) at room temperature. The mixture was stirred at room temperature for 30 min and then treated with silyl enol ether **4** (20 mmol). The reaction mixture was stirred for 12 h at room temperature and then quenched by a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 (50 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexanes/ethyl acetate = 10:1).

*8a-(Prop-2-yn-1-yl)hexahydronaphthalene-1,6(2H,7H)-dione (**5b**).* The general procedures for the DA/carbocyclization cascade cyclization reaction were followed with Et_2AlCl or M_2AlCl as the Lewis acid. Based on TLC analysis, both **5a** and **5b** were formed under the reaction condition, and **5b** (a white solid, 50−60%) was obtained as the major side product after workup. **5b**: mp = 110−111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 2.68−2.63 (m, 3H), 2.55−2.37 (m, 4H), 2.32−2.29 (m, 3H), 2.06 (s, 1H), 2.01−1.93 (m, 3H), 1.68−1.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 210.4, 79.0, 72.1, 51.4, 43.3, 42.6, 38.0, 37.6, 31.0, 26.4, 25.7, 22.8; IR (neat, cm^{-1}) 3292, 2952, 2927, 2869, 1718, 1706, 1458, 1436; HRMS (ESI/[M+Na]$^+$) calcd for $C_{13}H_{16}O_2Na^+$ 227.1048, found 227.1044. When the above reaction mixture was treated with $ZnBr_2$ (1.1 equiv) and was allowed to stirred at room temperature for 30 min, cyclized product **6a** (40−76%) was obtained.

*2-(2-Oxopropyl)cyclohex-2-enone (**7**).* The general procedures for the DA/carbocyclization cascade cyclization reaction were followed with $InCl_3$, $InBr_3$, or $In(OTf)_3$ as the Lewis acid. Compound **7** (a colorless oil, 60−90%) was obtained as the major side product after aqueous workup and silica gel flash column chromatography (hexanes/ethyl acetate = 20:1). 7: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (t, 1H, J = 4.1 Hz), 3.27 (s, 2H), 2.47 (dd, 2H, J = 2.9, 6.5 Hz), 2.45−2.38 (m, 2H), 2.20 (s, 3H), 2.10−1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 198.5, 148.5, 134.0, 44.1, 37.8, 29.9, 26.0, 22.9; HRMS (ESI/[M + H]$^+$) calcd for $C_9H_{13}O_2$ 153.0910, found153.0911.

For synthesis of **6a−j**, the general procedures for the DA/carbocyclization cascade cyclization reaction were followed with $ZnBr_2$ as the Lewis acid.

*6-Methylenehexahydro-4a,7-methanobenzo[7]annulene-4,8-(1H,5H)-dione (**6a**):* a white solid, 1.88 g, 8.6 mmol, 86% from **3a** and **4a**, a single diastereomer; mp = 80.0−80.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (t, J = 2.4 Hz, 1H), 5.00 (s, 1H), 3.40 (td, J = 17.6, 2.8 Hz, 1H), 3.32 (d, J = 5.2 Hz, 1H), 2.81 (dd, J = 16.0, 8.8 Hz, 1H), 2.48−2.26 (m, 5H), 2.11−2.04(m, 2H), 1.91−1.81 (m, 2H), 1.77−1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 207.5, 146.4, 109.4, 60.2, 57.3, 45.4, 41.3, 39.0, 37.5, 37.1, 29.6, 25.79; IR (neat, cm^{-1}) 2939, 2866, 1710, 1655, 1421, 1320, 1216, 1189, 1137, 896; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O_2$ 205.1229, found 205.1233.

*3-Methyl-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**6b**):* a white solid, 1.77 g, 8.1 mmol, 81% from **3b** and **4a**, dr = 8:1; major diastereomer, mp = 116.2−117.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, J = 2.0 Hz, 1H), 5.01 (s, 1H), 3.40 (td, J = 17.8, 2.6 Hz, 1H), 3.34 (d, J = 5.0 Hz, 1H), 2.81 (dd, J = 16.4, 8.6 Hz, 1H), 2.54 (td, J = 12.6, 6.2 Hz, 1H), 2.45−2.33 (m, 2H), 2.27 (dddd, J = 10.0, 8.4, 4.0, 2.0 Hz, 1H), 2.14−2.02 (m, 2H), 1.91−1.86 (m, 2H), 1.68 (ddd, J = 14.0, 6.8, 3.8 Hz, 1H), 1.60−1.52 (m, 1H), 1.42 (dq, J = 13.2, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 207.6, 146.3, 109.3, 60.2, 57.2, 46.2, 41.9, 41.3, 37.6, 37.0, 35.1, 29.7, 14.6; IR (neat, cm^{-1}) 2957, 2939, 2872, 1707, 1652, 1472, 1223, 1162, 914; HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{19}O_2$ 219.1385, found 219.1381.

*2-Methyl-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**6c**):* a white solid, 1.92 g, 8.8 mmol, 88% from **3c** and **4a**, a single diastereoisomer; mp = 118.8−119.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.99 (s, 1H), 3.36−3.30 (m, 2H), 2.79 (dd, J = 16.4, 8.6 Hz, 1H), 2.64 (dd, J = 13.8, 6.0 Hz, 1H), 2.56−2.27 (m, 4H), 2.16 (d, J = 13.8 Hz, 1H), 2.12−1.92 (m, 2H), 1.87 (dd, J = 11.6, 4.5 Hz, 1H), 1.49 (d, J = 14.1 Hz, 1H), 1.00 (dd, J =

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18.8, 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 207.8, 146.2, 109.4, 59.8, 56.9, 45.1, 40.8, 39.7, 37.4, 36.8, 35.3, 30.0, 19.1; IR (neat, cm^{-1}) 2970, 2921, 2884, 1704, 1655, 1469, 1433, 1381, 1317, 1231, 1182, 1146, 938; HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{19}O_2$ 219.1385, found 219.1393.

*1-Methyl-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**6d**):* a white solid, 1.86 g, 8.5 mmol, 85% from **3d** and **4a**, dr = 16:1; major diastereomer, mp = 74.1−75.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.98 (s, 1H), 3.40 (dd, J = 18.0, 2.0 Hz, 1H), 3.30 (d, J = 4.6 Hz, 1H), 2.65 (dd, J = 16.6, 8.0 Hz, 1H), 2.53 (dt, J = 14.1, 6.0 Hz, 1H), 2.40−2.25 (m, 4H), 2.05 (ddd, J = 13.1, 5.6, 3.2 Hz, 1H), 1.99−1.80 (m, 3H), 1.51−1.36 (m, 1H), 1.02 (dd, J = 22.4, 8.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 207.8, 146.4, 109.2, 59.8, 56.6, 51.9, 38.9, 38.0, 37.9, 37.4, 34.8, 31.9, 19.5; IR (neat, cm^{-1}) 2964, 2933, 2884, 1710, 1655, 1460, 1435, 1326, 1173, 1000, 896; HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{19}O_2$ 219.1385, found 219.1392.

*9a-Methyl-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**6e**):* a white solid, 1.75 g, 8.0 mmol, 80% from **3e** and **4a** (with 2 additional equiv of **4a** and stirring for 24 h), a single diastereomer; mp = 117.4−118.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.99 (s, 1H), 3.32 (d, J = 4.7 Hz, 1H), 3.06 (dd, J = 18.4, 2.6 Hz, 1H), 2.69−2.39 (m, 4H), 2.32 (ddd, J = 14.2, 3.4, 1.6 Hz, 1H), 2.19 (dt, J = 13.6, 5.2 Hz, 1H), 2.06 (d, J = 12.0 Hz, 1H), 2.00−1.89 (m, 3H), 1.37 (dd, J = 14.0, 2.0 Hz, 1H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 207.6, 146.7, 108.9, 61.1, 58.8, 50.1, 43.9, 39.0, 37.9, 34.1, 33.0, 22.8, 22.2; IR (neat, cm^{-1}) 2970, 2933, 2866, 1713, 1698, 1655, 1454, 1436, 1420, 1323, 1262, 1158, 1061, 893, 747; HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{19}O_2$ 219.1385, found 219.1389.

*1,1-Dimethyl-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**6f**):* a white solid, 1.86 g, 8.0 mmol, 80% from **3f** and **4a** (with 2 additional equiv of **4a** and stirring for 24 h, a single diastereomer); mp = 39.6−40.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (d, J = 1.2 Hz, 1H), 4.97 (s, 1H), 3.28 (d, J = 4.8 Hz, 1H), 3.14 (td, J = 17.2, 3.0 Hz, 1H), 2.67−2.47 (m, 2H), 2.42−2.32 (m, 1H), 2.29−2.23 (m, 3H), 2.00−1.93 (m, 2H), 1.90−1.68 (m, 2H), 1.00 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 208.6, 145.8, 109.9, 58.5, 55.1, 51.4, 43.0, 38.3, 37.2, 36.8, 35.8, 34.1, 30.7, 20.8; IR (neat, cm^{-1}) 2970, 2884, 1710, 1659, 1469, 1439, 1226, 1180, 1152, 887; HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{21}O_2$ 233.1542, found 233.1532.

*5-((tert-Butyldimethylsilyl)oxy)-6-methylenehexahydro-4a,7-methanobenzo[7]annulene-4,8(1H,5H)-dione (**6g**):* an off-white amorphous solid, 2.5 g, 7.5 mmol, 75% from **3g** and **4a**, dr = 7:1; major diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (d, J = 2.0 Hz, 1H), 5.19 (s, 1H), 5.14 (dd, J = 2.8, 0.8 Hz, 1H), 3.25 (d, J = 4.8 Hz, 1H), 3.05 (dd, J = 16.4, 8.8 Hz, 1H), 2.74−2.70 (m, 1H), 2.43−2.28 (m, 3H), 2.07−1.98 (m, 2H), 1.86−1.64 (m, 4H), 0.90 (s, 9H), 0.24 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 208.4, 150.5, 110.8, 74.3, 59.9, 41.6, 39.1, 36.6, 34.4, 29.6, 29.0, 25.8, 24.7, 18.0, −4.2, −4.9; IR (neat, cm^{-1}) 2958, 2939, 2866, 1707, 1475, 1250, 1140, 1122, 1094, 865, 838, 777; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{31}O_3Si$ 335.2042, found 335.2049.

*4-Methylenehexahydro-1H-3,5a-methanoheptalene-2,6(3H,7H)-dione (**6h**):* an off-white amorphous solid, 1.79 g, 8.2 mmol, 82% from **3h** and **4a**, a single diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (d, J = 1.4 Hz, 1H), 4.93 (s, 1H), 3.23 (d, J = 4.8 Hz, 1H), 2.87−2.60 (m, 2H), 2.55 (s, 2H), 2.48−2.44 (m, 1H), 2.41−2.18 (m, 2H), 2.14−1.72 (m, 4H), 1.68−1.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 208.4, 145.4, 110.1, 58.3, 58.0, 43.9, 43.5, 41.9, 41.2, 35.0, 33.2, 28.7, 25.7; IR (neat, cm^{-1}) 2933, 2866, 1704, 1655, 1451, 1332, 1219, 1173, 1651, 914, 890; HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{19}O_2$ 219.1385, found 219.1392.

*10,10-Dimethyl-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**6i**):* a white solid, 1.84 g, 7.9 mmol, 79% from **3a** and **4b**, a single diastereomer; mp = 74.8−76.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (t, J = 2.2 Hz, 1H), 4.99 (s, 1H), 3.73 (td, J = 18.0, 2.8 Hz 1H), 2.95−2.81 (m, 2H), 2.61−2.47 (m, 1H), 2.33 (ddd, J = 14.6, 10.2, 4.7 Hz, 2H), 2.17 (dd, J = 18.3, 3.4 Hz, 2H), 2.11−1.93 (m, 2H), 1.76−1.61 (m, 2H), 1.26 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 208.3, 144.6, 110.4, 72.4, 60.7, 46.6, 45.7, 41.6, 41.1, 40.2, 31.9, 25.6, 25.1, 24.3; IR (neat, cm^{-1}) 2957, 2872, 1692, 1652, 1460, 1262, 1222, 1173, 890; HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{21}O_2$ 233.1542, found 233.1525.

*7-Methyl-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**6j**):* a white solid, mp = 76.6−77.6 °C, 1.99 g, 9.1 mmol, 91% from **3a** and **4c**, a single diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.89 (t, J = 2.4 Hz, 1H), 3.53 (td, J = 17.8, 2.8 Hz, 1H), 2.82 (dd, J = 16.4, 8.6 Hz, 1H), 2.53−2.25 (m, 5H), 2.18−2.02 (m, 2H), 1.94−1.79 (m, 1H), 1.79−1.65 (m, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 208.3, 151.0, 107.7, 59.1, 55.4, 45.7, 44.1, 41.8, 38.9, 38.8, 29.4, 25.7, 16.5; IR (neat, cm^{-1}) 2933, 2866, 1707, 1652, 1433, 1323, 1253, 1210, 1146, 1058, 890; HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{19}O_2$ 219.1385, found 219.1376.

*6-Methylene-1,2,5,6,7,9a-hexahydro-4a,7-methanobenzo[7]-annulene-4,8-diyl-bis(oxy)bis(trimethylsilane) (**18a**).* To a solution of **6a** (10.2 g, 50 mmol), hexamethyldisilazane (42 mL, 200 mmol), and NaI (22.5g, 150 mmol) in CH_3CN (50 mL) was added TMSCl (1.87 g, 27.4 mmol) at room temperature. The reaction mixture was stirred for 1 h and then diluted with hexanes (250 mL) and quenched by water (50 mL). The aqueous layer was extracted with hexanes (100 mL × 3), and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to give a yellow oil as the crude product, which was used without further manipulations.

*6-Methylene-1,2,5,6,7,9a-hexahydro-4a,7-methanobenzo[7]-annulene-4,8-diyl-bis(oxy)bis(triethylsilane) (**18b**) and 6-Methylene-1,2,5,6,7,9a-hexahydro-4a,7-methanobenzo[7]annulene-4,8-diyl-bis(oxy)bis(tert-butyldimethylsilane) (**18c**).* To a solution of **6a** (2.04 g, 10 mmol) in CH_2Cl_2 (100 mL) and triethylamine (5.5 mL, 40 mmol) at 0 °C was added TESOTf or TBSOTf (25 mmol). The reaction mixture was stirred at 0 °C for 1 h and then quenched by brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. Compound **18b** was used without further manipulations, and compound **18c** was purified by silica gel flash column chromatography (hexanes/ethyl acetate = 99:1 with 3% Et_3N) to give a white solid (4.33 g, 10 mmol, 100%) as the product. **18c**: mp = 75.8−76.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.87 (d, J = 4.4 Hz, 1H), 4.80 (s, 1H), 4.59 (s, 1H), 4.47 (d, J = 4.0 Hz, 1H), 2.99 (d, J = 12.8 Hz, 1H), 2.67 (d, J = 4.4 Hz, 1H), 2.16−1.94 (m, 4H), 1.772 (dd, J = 10.4, 4.4 Hz, 1H), 1.60−1.53 (m, 2H), 1.39−1.28 (m, 2H), 0.94 (s, 9H), 0.92 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.3, 154.8, 152.9, 104.3, 103.3, 101.8, 50.4, 46.6, 44.7, 40.2, 35.9, 28.5, 25.74, 25.6, 24.1, 18.2, 17.9, −4.1, −4.3, −4.9, −5.0; IR (neat, cm^{-1}) 2964, 2933, 2866, 1662, 1470, 1348, 1253, 1198, 1171, 1088, 1040, 1006, 890, 832, 777; HRMS (ESI/[M + H]$^+$) calcd for $C_{25}H_{45}O_2Si_2$ 433.2958, found 433.2974.

*3-Hydroxy-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**19**).* To a solution of **18c** (10.8 g, 25 mmol), $NaHCO_3$ (2.1 g, 25 mmol) in CH_2Cl_2 (250 mL), and MeOH (250 mL) was added monoperoxyphthalic acid magnesium salt hexahydrate (MMPP) (6.8 g, 13.7 mmol) at room temperature. The resulting mixture was stirred for 2−4 h. After TLC analysis showed the consumption of the starting materials, the reaction mixture was quenched by addition of a saturated $Na_2S_2O_3$ aqueous solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (150 mL × 3), and the combined organic extracts were washed with a 2 N HCl aqueous solution, a saturated $NaHCO_3$ aqueous solution, and brine and then concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 2:1) of the residue gave a white solid (4.40 g, 20.0 mmol, 90%) as the product. **19**: mp = 138.8−138.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (t, J = 2.0 Hz, 1H), 5.05 (s, 1H), 4.30 (m, 1H), 3.59 (d, J = 3.2 Hz, 1H), 3.42 (td, J = 18.0, 2.8 Hz, 1H), 3.37 (d, J = 5.2 Hz, 1H), 2.79 (dd, J = 16.8, 8.8 Hz, 1H), 2.49−2.42 (m, 2H), 2.37−2.26 (m, 2H), 2.10 (d, J = 8.4 Hz, 1H), 1.96−1.87 (m, 1H), 1.76−1.71 (m, 1H), 1.61−1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 206.6, 144.8, 110.1, 72.7, 59.8, 55.9, 45.8, 40.7, 37.4, 36.6, 35.4, 27.4;

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IR (neat, cm^{-1}) 3391, 2939, 1716, 1695, 1439, 1104, 976, 899, 865; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O_3$ 221.1178, found 221.1180.

*6-Methylene-6,7,9,9a-tetrahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**12**).* To a stirred solution of **19** (6.60 g, 30.0 mmol) in THF (600 mL) was added $NaBH_4$ (0.39 g, 10.5 mmol) slowly in portions at −78 °C. The resulting mixture was stirred at −78 °C for 30 min and then warmed to −20 °C slowly. After TLC showed consumption of **19**, the reaction was quenched by addition of a saturated NH_4Cl aqueous solution (50 mL) at −20 °C. The aqueous phase was extracted with ethyl acetate (300 mL × 3), and the combined organic extracts were washed with brine (50 mL × 2), dried over $MgSO_4$, filtered, and concentrated to give a pale yellow oil as the crude product (a mixture of diol diastereomers), which was used without further manipulations. To a solution of the crude product (6.60 g, 30.0 mmol) in toluene (600 mL) were added triphenylphosphine (31.4 g, 120 mmol), imidazole (8.2 g, 120 mmol), and iodine (22.9 g, 90 mmol). The mixture was heated under reflux for 5 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (500 mL) and washed successively with a 10% sodium thiosulfate aqueous solution, a saturated $NaHCO_3$ aqueous solution, and brine, and dried over $MgSO_4$. After removal of the volatiles, silica gel flash column chromatography (hexanes/ethyl acetate = 20:1) of the residue gave (4.2 g, 22 mmol, 75%) a colorless oil as the product. **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (td, J = 10.0, 4.4 Hz, 1H), 5.46 (td, J = 8.0, 2.0 Hz, 1H), 5.01 (s, 1H), 4.93 (s, 1H), 3.19 (s, 1H), 2.84 (dd, J = 17.2, 8.0 Hz, 1H), 2.52−2.41 (m, 1H), 2.07−1.83 (m, 6H), 1.62−1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 148.3, 132.9, 127.6, 108.7, 59.3, 45.7, 43.9, 42.0, 40.5, 39.6, 28.3, 25.5; IR (neat, cm^{-1}) 2957, 2933, 2897, 2866, 1723, 1473, 1259, 1070, 1006, 838, 783; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O$ 189.1279, found 189.1269.

*9-Hydroxy-6-methylene-1,2,6,7,9,9a-hexahydro-4a,7-methanobenzo[7]annulen-8(5H)-one (**20**) and 8-Hydroxy-6-methylene-1,5,6,7,8,9a-hexahydro-4a,7-methanobenzo[7]annulen-9(2H)-one (**22**).* To a solution of **12** (3.76 g, 20 mmol) in CH_2Cl_2 (100 mL) and triethylamine (11 mL, 80 mmol) at 0 °C was added TBSOTf (11.4 mL, 30 mmol). The reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched by brine, separated, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 99:1 with 5% Et_3N) of the residue gave a yellow oil as the crude product, which was used without further manipulations. To a solution of the crude silyl enol ether in CH_2Cl_2 (200 mL) and MeOH (100 mL) with $NaHCO_3$ (3.36, 40 mmol) at room temperature was added MMPP (5.94 g, 12 mmol). After stirring at room temperature for 2−4 h, then reaction mixture was quenched by addition of a saturated $Na_2S_2O_3$ aqueous solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (300 mL × 3), and the combined organic extracts were washed with brine and then concentrated. The residue was then dissolved in THF (100 mL) and MeOH (10 mL) and was treated with a 2 M aqueous HCl solution (100 mL) at room temperature. The mixture was stirred at room temperature for 2 h and quenched by addition of a saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with diethyl ether (200 mL × 3), and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue gave a yellow oil (3.45 g, 16.9 mmol, 85%) as the product. **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.48 (td, J = 9.6, 2.0 Hz, 1H), 5.05 (t, J = 2.0 Hz,1H), 4.96 (s, 1H), 4.58 (d, J = 8.8 Hz, 1H), 3.35 (d, J = 4.8 Hz, 1H), 3.21 (s, 1H), 2.62−2.47 (m, 3H), 2.10−2.02 (m, 3H), 1.95−1.84 (m, 2H), 1.11−1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 147.7, 132.0, 128.4, 109.2, 71.7, 56.5, 49.5, 44.9, 44.8, 42.0, 25.3, 18.3; IR (neat, cm^{-1}) 3433, 2921, 1716, 1442, 1226, 899, 734, 704; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O_2$ 205.1229, found 205.1240. When the above reaction mixture was stirred in the HCl/THF/methanol mixture for 24 h and then quenched by saturated aqueous $NaHCO_3$ solution. Another yellow oil (3.45 g, 16.9 mmol, 85%) was obtained as the product using the same workup procedures. **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (td, J = 12.0, 3.0 Hz, 1H), 5.50 (td, J = 12.0, 3.0 Hz, 1H), 5.09 (t, J = 1.5 Hz,1H), 4.95 (s, 1H), 4.24 (t, J = 3.0 Hz, 1H), 3.61 (d, J = 3.0 Hz, 1H), 2.94 (t, J = 3.0 Hz, 1H), 2.44−2.34 (m, 2H), 2.22−2.12 (m, 3H), 2.06−2.01 (m, 1H), 1.95−1.88 (m, 1H), 1.85−1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 146.4, 132.3, 127.5, 110.8, 78.1, 55.9, 48.2, 46.4, 45.8, 40.1, 25.3, 24.1; IR (neat, cm^{-1}) 3482, 2933, 1704, 1436, 1381, 1088, 884, 701; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O_2$ 205.1229, found 205.1237.

*6-Methylene-9-oxo-1,2,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]annulen-8-yl acetate (**23**).* To a solution of **22** (2.04 g, 10 mmol) in CH_2Cl_2 (100 mL) with triethylamine (5.6 mL, 40 mmol) at room temperature was added acid anhydride (1.8 mL, 20 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched with saturated $NaHCO_3$ aqueous solution (30 mL). The aqueous layer was extracted by diethyl ether (50 mL × 3), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue afford a colorless oil (2.33 g, 9.5 mmol, 95%) as the product. **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (td, J =10.0, 2.8 Hz, 1H), 5.49 (td, J = 10.0, 2.8 Hz, 1H), 5.31 (d, J = 3.6 Hz,1H), 5.11 (s, 1H), 5.04 (s, 1H), 2.93 (t, J = 4.6 Hz, 1H), 2.44−2.38 (m, 2H), 2.28 (d, J = 16.8 Hz, 1H), 2.18 (s, 3H), 2.17−2.06 (m, 3H), 1.99−1.94 (m, 1H), 1.85−1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 170.1, 146.5, 132.0, 127.8, 111.6, 78.4, 56.9, 46.4, 45.8, 44.9, 40.2, 25.3, 24.4, 20.7; IR (neat, cm^{-1}) 2933, 2860, 1750, 1726, 1432, 1375, 1235, 1070, 1043, 1024, 738, 710; HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{19}O_3$ 247.1334, found 247.1316.

*6-Methylene-1,5,6,7,8,9a-hexahydro-4a,7-methanobenzo[7]-annulen-9(2H)-one (**11**).* To a stirred solution of **23** (1.23 g, 5 mmol) in THF (degassed, 67 mL) and MeOH (33 mL) at 0 °C was added SmI_2 (a 0.1 M solution in THF, 110 mL). The resulting mixture was stirred at 0 °C for 20 min and was quenched with water (100 mL) and extracted with diethyl ether (100 mL × 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 20:1) of the residue afforded a yellow oil (0.89 g, 4.7 mmol, 95%) as the product. **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (td, J =10.8, 2.8 Hz, 1H), 5.47 (td, J = 10.0, 2.4 Hz, 1H), 4.97 (s,1H), 5.11 (s, 1H), 4.93 (s, 1H), 2.90 (d, J = 3.6 Hz, 1H), 2.54−2.23 (m, 4/H), 2.15−2.11 (m, 2H), 1.86−1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 152.8, 133.3, 127.4, 108.3, 56.9, 49.8, 46.9, 44.2, 40.7, 40.6, 25.5, 25.0; IR (neat, cm^{-1}) 2933, 1735, 1646, 1433, 1366, 1247, 1037, 874, 698; HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{19}O_3$ 247.1334, found 247.1316; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O$ 189.1279, found 189.1263.

*8-Methyl-3,4,4a,5,6,7,8,9-octahydro-5,8-epoxy-7,9a-methanobenzo[7]annulene (**10**, Snider's Intermediate).* To a stirred solution of **11** (564 mg, 3 mmol) in CH_2Cl_2 (50 mL) was added K-selectride (a 1.0 M solution in THF, 18 mL, 18 mmol) at −78 °C, and the reaction mixture was allowed to warm to 0 °C and stirred for 1.5 h. The reaction was then quenched with a saturated NH_4Cl aqueous solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a yellow oil as the crude alcohol product, which was used without further manipulations. To a stirred solution of the crude alcohol product (570 mg, 3 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (10 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 30:1) of the residue afforded a colorless oil (484 mg, 85%) as the product. Snider's intermediate **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (td, J =10.8, 3.6 Hz, 1H), 5.33 (td, J = 10.0, 2.0 Hz, 1H), 4.14 (d, J = 6.8 Hz, 1H), 2.15−2.09 (m, 3H), 1.91−1.74 (m, 4H), 1.58−1.42 (m, 5H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ = 133.13, 126.7, 86.7, 80.6, 52.6, 45.5, 44.8, 44.6, 43.5, 38.3, 26.2, 23.3, 22.2; IR (neat, cm^{-1}) 2941, 2865, 1709, 1473, 1447, 1377, 1326, 1090, 997, 823; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{19}O$ 191.1436, found 191.1433.

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*3-Bromo-6-methylenehexahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**24**).* To a solution of **18c** (4.32 g, 10 mmol) in THF (200 mL) was added NBS (1.96 g, 11 mmol) at 0 °C. The mixture was stirred until TLC analysis showed the consumption of the starting material (about 2 h). The mixture was then quenched with a 2 N HCl aqueous solution. The aqueous layer was extracted with diethyl ether (200 mL × 3), and the combined organic extracts were washed with a saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 10:1) of the residue gave a white solid (2.52 g, 9 mmol, 90%) as the product. **24**: mp = 75.8−76.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 1H), 5.06 (s, 1H), 4.80 (dd, J = 13.2, 6.0 Hz, 0.5H), 4.66 (dd, J = 12.8, 6.0 Hz, 0.5H), 3.49−3.43 (m, 1H), 3.38 (d, J = 5.2 Hz, 1H), 2.82 (dd, J = 16.8, 8.8 Hz, 1H), 2.69−2.64 (m, 1H), 2.59−2.52 (m, 1H), 2.43 (d, J = 3.6 Hz, 1H), 2.39−2.34 (m, 2H), 2.18−1.95 (m, 4H), 1.84−1.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 206.4, 201.8, 201.2, 144.9, 144.8, 110.1, 110.0, 62.0, 59.8, 59.8, 57.5, 57.4, 53.8, 45.2, 45.1, 40.6, 38.3, 38.0, 38.0, 37.3, 36.6, 36.5, 30.5, 29.4; IR (neat, cm^{-1}) 2945, 2870, 1713, 1655, 1423, 1322, 1224, 1190, 1140, 895; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{16}O_2Br$ 283.0334, found 283.0370.

*6-Methylene-6,7,9,9a-tetrahydro-4a,7-methanobenzo[7]-annulene-4,8(1H,5H)-dione (**15**).* Procedures with **24** as the starting material: To a stirred solution of **24** (1.41 g, 0.5 mmol) in DMF (5 mL) were added LiBr (0.26 g, 3 mmol) and Li_2CO_3 (0.22 g, 3 mmol). The resulting mixture was stirred at 120 °C until TLC analysis showed consumption of the starting material (about 2 h). The mixture was then poured into cool water (10 mL), and the precipitate was collected by filtration. Silica gel flash column chromatography (*n*hexanes/EtOAc = 4:1) of the precipitate afforded an amorphous solid (71 mg, 70%) as the product. **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.89 (td, J = 10.0, 4.0 Hz, 1H), 6.20−6.02 (d, J = 10.8 Hz, 1H), 5.11 (s, 1H), 5.03 (s, 1H), 3.58 (td, J = 17.6, 2.8 Hz, 1H), 3.35 (d, J = 5.0 Hz, 1H), 2.84 (dd, J = 16.0, 8.0 Hz, 1H), 2.63 (dd, J = 16.0, 8.0 Hz, 1H), 2.50−2.29 (m, 1H), 2.22 (dd, J = 12.0, 1.6 Hz, 1H), 2.06 (d, J = 16.0 Hz, 1H), 1.83−1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.5, 199.2, 147.5, 146.4, 129.2, 109.2, 59.8, 53.0, 40.6, 40.4, 37.4, 35.9, 30.5; IR (neat, cm^{-1}) 2951, 2914, 2855, 1710, 1670, 1418, 1387, 1311, 1219, 1183, 899, 801; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{15}O_2$ 203.1072, found 203.1061. General procedures with **6a** as the starting material: To a stirred 0.2 M solution of **6a** in DMSO or ethyl acetate was added IBX (2−4 equiv). The solution was stirred at 80 °C until TLC analysis showed the consumption of starting material. The reaction mixture was cooled to room temperature and diluted with diethyl ether. The organic layer was washed with a 5% $NaHCO_3$ aqueous solution, water, and brine, and then dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (*n*-hexanes/EtOAc = 4:1) of the residue afforded an amorphous solid (30−40%) as the product. General procedures with **18a−c** as the starting material: To the crude **18a−c** was added a 1:1 IBX/NMO (2−10 equiv) solution in DMSO (0.2 M for **18a-c**) in one portion at ambient temperature. The mixture was stirred at 45 °C until TLC analysis showed consumption of the starting material. The reaction mixture was then diluted with a 5% $NaHCO_3$ aqueous solution and extracted with diethyl ether (×3). The combined organic extracts was filtered through a pad of Celite and washed with saturated aqueous $NaHCO_3$ solution, water, and brine. After drying over $MgSO_4$ and filtration, the volatiles were removed in vacuo. Silica gel flash column chromatography (*n*-hexanes/EtOAc = 4:1) of the residue afforded an amorphous solid (20−57%) as the product along with **6a** (10−70%) being recovered.

*6-Methylene-1,4,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]-annulene-4,8-diol (**25**).* To a solution of **15** (2.02 g, 10 mmol) in MeOH (100 mL) was added $CeCl_3{\cdot}7H_2O$ (3.72 g, 10 mmol) at 0 °C. The reaction mixture was cooled to −78 °C and treated with $NaBH_4$ (0.37g, 10 mmol). After stirring at −78 °C for 10 min, the reaction mixture was concentrated. The residue was dissolved in diethyl ether (100 mL) and washed by a saturated $NaHCO_3$ aqueous solution (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 4:1) of the residue gave a colorless oil (2.00 g, 9.7 mmol, 97%) as the product. **25**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.73−5.63 (m, 1H), 5.59 (dd, J = 10.0, 2.0 Hz, 1H), 4.97 (d, J = 1.6 Hz, 2H), 4.17 (s, 1H), 3.91−3.76 (m, 1H), 2.74−2.68 (m, 2H), 2.10−1.97 (m, 3H), 1.84−1.63 (m, 4H), 1.49−1.35 (m, 3H), 1.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.0, 130.7, 127.6, 106.8, 70.3, 69.0, 50.8, 46.1, 39.8, 38.0, 34.7, 29.6, 28.2; IR (neat, cm^{-1}) 3427, 2927, 2848, 1652, 1457, 1432, 1076, 1046, 871; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{19}O_2$ 207.1385, found 207.1388.

*6-Methylene-1,4,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]-annulene-4,8-diyl diacetate (**26**).* To a solution of **25** (1.03 g, 5 mmol) in CH_2Cl_2 (50 mL) with triethylamine (4.2 mL, 30 mmol) at room temperature was added acid anhydride (1.1 mL, 12 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched with a saturated $NaHCO_3$ aqueous solution (20 mL). The aqueous layer was extracted by diethyl ether (20 mL × 3), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue afforded a white solid (1.44 g, 5 mmol, 99%) as the product. **26**: mp = 99.6−100.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (tdd, J = 9.4, 4.4, 2.2 Hz, 1H), 5.59−5.43 (m, 1H), 5.38 (s, 1H), 5.03−4.85 (m, 3H), 2.75 (d, J = 2.8 Hz, 1H), 2.37 (td, J = 16.9, 2.4 Hz, 1H), 2.20−2.03 (m, 9H), 1.99−1.89 (m, 1H), 1.82−1.66 (m, 2H), 1.59−1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.6, 148.3, 128.4, 127.0, 108.0, 72.3, 72.0, 47.0, 44.4, 39.7, 37.8, 29.9, 29.6, 29.4, 21.2, 21.1; IR (neat, cm^{-1}) 2957, 2914, 1735, 1655, 1460, 1433, 1366, 1238, 1037, 957, 884; HRMS (ESI/[M + H]$^+$) calcd for $C_{17}H_{23}O_4$ 291.1596, found 291.1604.

*8-Hydroxy-6-methylene-5,6,7,8,9,9a-hexahydro-4a,7-methanobenzo[7]annulen-4(1H)-one (**28**).* To a solution of **25** (1.03 g, 5 mmol) in CH_2Cl_2 (50 mL) was added MnO_2 (8.7 g, 100 mmol). The reaction mixture was heated under reflux for 12 h. After cooling to room temperature, the mixture was filtered and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 4:1) of the residue afford a colorless oil (0.98 g, 4.8 mmol, 95%) as the product. **28**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (ddd, J = 10.0, 5.6, 2.2 Hz, 1H), 6.03 (ddd, J = 10.0, 2.8, 1.0 Hz, 1H), 5.01−5.00 (m, 2H), 3.93−3.77 (m, 1H), 3.31 (td, J = 17.4, 2.6 Hz, 1H), 2.82−2.66 (m, 1H), 2.57−2.39 (m, 1H), 2.33 (td, J = 19.5, 5.4 Hz, 1H), 2.22 (td, J = 11.8, 6.0 Hz, 1H), 2.11−1.96 (m, 1H), 1.83 (ddd, J = 19.4, 12.8, 4.0 Hz, 2H), 1.68 (d, J = 10.4 Hz, 1H), 1.67 (s, 1H), 1.42 (ddd, J = 13.8, 11.2, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 148.7, 148.0, 129.2, 107.3, 68.6, 53.2, 50.3, 39.2, 37.8, 35.1, 34.5, 30.1; IR (neat, cm^{-1}) 3494, 3055, 2988, 2927, 1735, 1671, 1372, 1268, 1247, 1049, 741, 704; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O_2$ 205.1229, found 205.1237.

*8-((tert-Butyldimethylsilyl)oxy)-6-methylene-5,6,7,8,9,9a-hexahydro-4a,7-methanobenzo[7]annulen-4(1H)-one (**29**).* To a stirred solution of **28** (204 mg, 1 mmol) in CH_2Cl_2 (10 mL) were added imidazole (170 mg, 2.5 mmol) and TBSCl (181 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2), and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 10:1) of the residue gave a white solid (318 mg, 0.99 mmol, 99%) as the product. **29**: mp = 95.0−95.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (ddd, J = 10.0, 5.6, 2.0 Hz, 1H), 6.08−5.91 (m, 1H), 4.94 (t, J = 6.4 Hz, 2H), 3.85 (ddd, J = 10.53, 5.69, 3.02 Hz, 1H), 3.25 (td, J = 17.10, 2.63 Hz, 1H), 2.60 (t, J = 1.2 Hz, 1H), 2.45 (tdd, J = 19.4, 11.7, 2.4 Hz, 1H), 2.29 (td, J = 19.6, 5.4 Hz, 1H), 2.17 (td, J = 11.6, 5.79 Hz, 1H), 2.00 (dd, J = 17.2, 1.8 Hz, 1H), 1.89−1.72 (m, 1H), 1.70−1.43 (m, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 148.0, 147.5, 129.2, 107.8, 69.9, 53.2, 50.4, 39.2, 37.9, 35.4, 34.3, 30.4, 25.7, 18.1, −4.6, −4.7; IR (neat, cm^{-1}) 2957, 2933, 2890, 2860, 1683, 1667, 1469, 1390, 1250, 1137, 1106, 1088, 1070, 884, 869, 832, 774; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{31}O_2Si$ 319.2093, found 319.2100.

*6-((tert-Butyldimethylsilyl)oxy)-4-methyleneoctahydro-2a,5-methanocyclohepta[4,5]benzo[1,2-b]oxiren-2(1aH)-one (**30**).* To a solution of **29** (3.18 g, 10 mmol) in MeOH (100 mL) were added a

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30% H_2O_2 aqueous solution (1.53 mL, 25 mmol) and a 6 N NaOH aqueous solution (1.86 mL, 10.5 mmol). The reaction was stirred at room temperature for 1.5 h. Then the solution was quenched with a saturated $Na_2S_2O_3$ aqueous solution (50 mL). The mixture was extracted with diethyl ether (100 mL × 3) and washed with brine (40 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue afforded a white solid (3.2 g, 9.6 mmol, 96%) as the product. **30**: mp = 108.8−109.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.94 (s, 1H), 3.73 (ddd, J = 10.8, 5.6, 3.0 Hz, 1H), 3.52 (t, J = 2.7 Hz, 1H), 3.21 (d, J = 3.6 Hz, 1H), 3.10 (td, J = 16.8, 2.6 Hz, 1H), 2.60 (s, 1H), 2.21−2.16 (m, 2H), 2.11−2.04 (m, 2H), 1.74 (dd, J = 11.6, 2.4 Hz, 1H), 1.69−1.55 (m, 1H), 1.55−1.42 (m, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 147.1, 108.1, 69.8, 53.7, 53.4, 53.3, 51.0, 39.3, 37.6, 33.2, 30.6, 27.51, 25.7, 18.0, −4.7, −4.7; IR (neat, cm^{-1}) 2945, 2878, 2854, 1695, 1247, 1107, 1091, 884, 832, 771; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{31}O_3Si$ 335.2042, found 335.2050.

*8-((tert-Butyldimethylsilyl)oxy)-6-methylene-1,2,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]annulen-2-ol (**31**).* To a solution of **30** (3 g, 9 mmol) in MeOH (80 mL) was added $NH_2NH_2{\cdot}H_2O$ (0.95 mL, 18 mmol) at 0 °C. After stirring for 15 min, AcOH (1.1 mL, 18 mmol) was added at 0 °C, and the resulting mixture was stirred at the same temperature for another 1.5 h; the reaction was then quenched by a saturated $NaHCO_3$ aqueous solution, and the mixture was extracted with diethyl ether (100 mL × 2). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue gave a yellow solid (2.67 g, 8.3 mmol, 93%) as the product. **31**: mp = 86.7−87.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75−5.66 (m, 2H), 4.94 (d, J = 10.8 Hz, 2H), 4.13 (d, J = 4.0 Hz, 1H), 3.72 (ddd, J = 10.8, 5.8, 3.0 Hz, 1H), 2.50 (s, 1H), 2.39−2.18 (m, 2H), 2.02−1.69 (m, 4H), 1.66 (dd, J = 19.2, 7.4 Hz, 1H), 1.56−1.36 (m, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 139.5, 127.4, 107.5, 70.9, 64.4, 50.2, 45.5, 44.1, 37.6, 36.1, 35.2, 34.3, 25.8, 18.1, −4.6, −4.7; IR (neat, cm^{-1}) 3354, 2933, 2853, 1478, 1250, 1106, 1076, 1012, 878, 832, 774; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{33}O_2Si$ 321.2250, found 321.2244.

*2-((4-Methoxybenzyl)oxy)-6-methylene-1,2,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]annulen-8-yl)oxy)dimethylsilane (**32**).* To a solution of **31** (1.60 g, 5 mmol) in anhydrous DMF (50 mL) was added NaH (a 60% dispersion in mineral oil, 600 mg, 15 mmol) at room temperature. The resulting solution was stirred at room temperature for 25 min and treated with PMBCl (2 mL, 15 mmol, 3 equiv). After stirring at the same temperature for 3 h, the reaction mixture was quenched by addition of a saturated NH_4Cl aqueous solution (50 mL). The resulting mixture was extracted with diethyl ether (100 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue gave a yellow oil (1.98 g, 4.5 mmol, 90%) as the product. **32**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.68 Hz, 2H), 6.88 (d, J = 8.41 Hz, 2H), 5.77−5.71 (m, 2H), 4.95 (d, J = 11.2 Hz, 2H), 4.50 (dd, J = 34.0, 11.6 Hz, 2H), 3.83 (t, J = 6.0 Hz, 1H), 3,77 (s, 3H), 3.75 (m, 1H), 2.50 (s, 1H), 2.30 (s, 2H), 2.06−1.97 (m, 1H), 1.86−1.70 (m, 3H), 1.53−1.39 (m, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 149.4, 139.8, 130.9, 129.1, 125.6, 113.4, 107.4, 71.1, 70.5, 70.1, 55.2, 50.3, 45.4, 44.2, 37.7, 35.4, 34.8, 32.5, 25.8, 18.1, −4.6, −4.7; IR (neat, cm^{-1}) 2939, 2854, 2836, 1610, 1515, 1463, 1302, 1253, 1174, 1079, 1037, 820; HRMS (ESI/[M + H]$^+$) calcd for $C_{27}H_{41}O_3Si$ 441.2825, found 441.2833.

*2-((4-Methoxybenzyl)oxy)-6-methylene-1,2,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]annulen-8-ol (**14**).* To a solution of **32** (1.76 g, 4 mmol) in anhydrous THF (20 mL) was added TBAF (a 1.0 M solution in THF, 12 mL, 12 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h and then quenched by addition of a saturated NH_4Cl aqueous solution (20 mL). The aqueous layer was extracted with diethyl ether (50 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 5:1) of the residue gave a yellow oil (1.30 g, 4 mmol, 100%) as the product. **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.4, 3.0 Hz, 2H), 6.88 (dd, J = 6.4, 2.0 Hz, 2H), 5.83−5.68 (m, 2H), 4.97 (s, 2H), 4.49 (dd, J = 27.8, 11.6 Hz, 2H), 3.89−3.76 (m, 1H), 3.76−3.65 (m, 5H), 2.62 (m, 1H), 2.39−2.22 (m, 2H), 2.02 (dd, J = 17.2, 7.4 Hz, 1H), 1.88−1.75 (m, 2H), 1.73−1.61 (m, 2H), 1.62−1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 150.5, 139.3, 130.9, 129.2, 125.9, 113.7, 106.9, 70.5, 70.2, 69.9, 55.2, 50.1, 45.3, 44.1, 37.4, 35.6, 34.9, 32.3; IR (neat, cm^{-1}) 3445, 3055, 2933, 2860, 1716, 1604, 1518, 1454, 1265, 1170, 1033, 887, 826, 737, 704; HRMS (ESI/[M + H]$^+$) calcd for $C_{21}H_{27}O_3$ 327.1960, found 327.1971.

*2-((4-Methoxybenzyl)oxy)-6-methylene-1,2,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]annulen-8-yl) S-methyl carbonodithioate (**33**).* To a stirred solution of **14** (1.02 g, 3.1 mmol) in dry THF (40 mL) was added sodium hydride (a 60% dispersion in mineral oil, 800 mg, 20 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 30 min. The mixture was treated with carbon disulfide (3.60 mL, 60.00 mmol) and heated under reflux for 1 h. The reaction mixture was allowed to cool to room temperature, then treated with methyl iodide (1.2 mL, 20 mmol) and stirred for 16 h. The reaction mixture was diluted with ethanol (8 mL), water (16 mL), and extracted with diethyl ether (50 mL × 3). The combined organic extracts were washed with a saturated NH_4Cl aqueous solution (20 mL) followed by brine and dried over Na_2SO_4. After filtration and removal of the volatiles, silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue gave a yellow oil (1.24 g, 2.96 mmol, 95%) as the product. **33**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.95−6.81 (m, 2H), 5.81−5.71 (m, 2H), 5.69 (dddd, J = 11.0, 8.8, 7.8, 3.5 Hz, 1H), 4.99 (d, J = 20.0 Hz, 2H), 4.50 (dd, J = 27.6, 11.6 Hz, 2H), 3.85 (t, J = 2.0 Hz, 1H), 3.81 (s, 3H), 2.99 (s, 1H), 2.54 (s, 3H), 2.37 (s, 2H), 2.18−2.03 (m, 2H), 1.93−1.76 (m, 3H), 1.63−1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 150.5, 139.3, 130.9, 129.2, 125.9, 113.7, 106.9, 70.5, 70.2, 69.9, 55.2, 50.1, 45.3, 44.1, 37.4, 35.6, 34.9, 32.3; IR (neat, cm^{-1}) 2951, 2933, 2866, 1732, 1616, 1515, 1457, 1244, 1232, 1207, 1046, 960, 930, 880, 820; HRMS (ESI/[M + H]$^+$) calcd for $C_{21}H_{27}O_3$ 327.1960, found 327.1971.

*3-Methylene-3,4,8,8a-tetrahydro-1H-2,4a-ethanonaphthalen-7(2H)-one (**13**, Nicolaou's Intermediate).* To a stirred solution of **33** (654 mg, 2 mmol) in benzene (200 mL) at room temperature were added n-Bu_3SnH (2.65 mL, 10 mmol) and AIBN (659 mg, 4 mmol). The mixture was heated under reflux for 4 h. During the course of heating, additional amounts of n-Bu_3SnH (607 μL, 10 mmol × 3) were added to ensure the completion of the reaction. After cooling to room temperature and removal of the volatiles, the residue was dissolved in diethyl ether and washed with a 1 N HCl aqueous solution (5 mL). The solution was brought to neutral condition by addition of a 1 N NaOH aqueous solution. The organic layer was separated, washed with brine, and concentrated to give a colorless oil as a crude product, which was used without further manipulations. To a solution of the crude product in CH_2Cl_2 (20 mL) and H_2O (0.1 mL) was added DDQ (0.91 g, 4 mmol) at room temperature. The mixture was stirred for 30 min and then quenched by a saturated $Na_2S_2O_3$ aqueous solution (10 mL). The aqueous layer was extracted by diethyl ether (20 mL × 2), and the combined organic extracts were washed with a saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was used without further manipulations. To a stirred solution of the crude product in CH_2Cl_2 (20 mL) at room temperature were added $NaHCO_3$ (0.50 g, 6 mmol) and Dess-Martin periodinane (1.27 g, 3 mmol). The reaction mixture was stirred at room temperature for 30 min, and then the solution was quenched with a saturated $Na_2S_2O_3$ aqueous solution (10 mL). The aqueous layer was extracted by diethyl ether (20 mL × 2), and the combined organic extracts were washed with a saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 20:1) of the residue gave a colorless oil (309 mg, 1.6 mmol, 82% in 3 steps from **33**) as the product. Nicolaou's intermediate (**13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, J = 10.0 Hz, 1H), 5.88 (d, J = 10.0 Hz, 1H), 4.84 (d, J = 1.7 Hz, 1H),

4.69 (d, J = 1.7 Hz, 1H), 2.48−2.40 (m, 2H), 2.36−2.29 (m, 2H), 2.19−2.08 (m, 2H), 2.03−1.96 (m, 1H), 1.82−1.68 (m, 3H), 1.55−1.48 (m, 1H), 1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 156.6, 148.8, 127.7, 106.8, 41.6, 40.8, 36.0, 35.5, 35.4, 34.8, 26.3, 24.4; IR (neat, cm^{-1}) 2941, 2864, 1680, 1430, 1273, 1236, 1162, 876, 766; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{17}O$ 189.1279, found 189.1287.

*6-Methylenedecahydro-4a,7-methanobenzo[7]annulene-4,8-diol (**34**).* To a stirred solution of **6a** (10.2 g, 50 mmol) in MeOH (250 mL) was added $NaBH_4$ (4.08 g, 110 mmol). The resulting mixture was stirred at room temperature for 2 h, and then the volatiles were removed under reduced pressure. Silica gel flash column chromatography (hexanes/ethyl acetate = 2:1) of the residue gave an off-white amorphous solid (10.09 g, 48.5 mmol, 97%, a mixture of diastereomer) as the product. The major diastereomer of **34** was obtained by washing of the amorphous solid with hexanes a few times. **34** (major diastereomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.90 (s, 1H), 3.72 (m, 1H), 3.46 (m, 1H), 2.74 (d, J = 6.4 Hz, 1H), 2.62 (s, 1H), 1.91−1.85 (m, 3H), 1.76−1.54 (m, 5H), 1.46−1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 106.5, 72.6, 69.8, 51.0, 48.7, 42.6, 39.8, 35.6, 32.0, 28.7, 28.3, 24.3; IR (neat, cm^{-1}) 3378, 2939, 2859, 1726, 1652, 1452, 1253, 1043, 874, 735; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{21}O_2$ 209.1542, found 209.1549. The stereochemistry of **34** was assigned by comparing the ^{1}H and ^{13}C NMR spectra with the product that obtained by TBAF deprotection of the major diastereomer of **34**.

*8-((tert-Butyldimethylsilyl)oxy)-6-methylenedecahydro-4a,7-methanobenzo[7]annulen-4-ol (**35**).* To a stirred solution of **34** (9.4 g of a mixture of diastereomers, 45 mmol) in CH_2Cl_2 (450 mL) were added imidazole (7.65 g, 112.5 mmol) and TBSCl (7.46 g, 49.5 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched by addition of a saturated $NaHCO_3$ aqueous solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 10:1) of the residue gave a white solid (11.6 g, 36 mmol, 80%, a roughly 3:1 diastereomeric mixture) as the product along with **34** (0.9 g, 4.3 mmol) being recovered. **35** (major diastereomer): mp = 73.3−74.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (d, J = 1.8 Hz, 1H), 4.88 (s, 1H), 3.78 (ddd, J = 10.8, 5.6, 3.0 Hz, 1H), 3.48 (d, J = 5.8 Hz, 1H), 2.71 (td, J = 16.6, 2.6 Hz, 1H), 2.54 (s, 1H), 1.92 (dd, J = 16.6, 1.6 Hz, 1H), 1.80−1.73 (m, 2H), 1.64−1.59 (m, 2H), 1.53−1.29 (m, 8H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 107.1, 72.9, 71.1, 51.2, 48.7, 42.6, 39.8, 35.4, 32.0, 29.1, 28.4, 25.80, 24.4, 18.1, −4.6, −4.7; IR (neat, cm^{-1}) 3397, 2957, 2933, 2890, 2860, 1659, 1473, 1463, 1372, 1253, 1110, 1082, 1055, 881, 863, 835, 771; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{35}O_2Si$ 323.2406, found 323.2413. **35** (minor diastereomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.81 (s, 1H), 3.82 (t, J = 4.0 Hz, 1H), 3.39 (dd, J = 7.2, 4.0 Hz, 1H), 2.73−2.69 (m, 2H), 2.06−1.81 (m, 4H), 1.71−1.66 (m, 2H), 1.57−1.32 (m, 8H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5 105.0, 73.8, 72.9, 50.2, 49.7, 41.7, 39.1, 33.0, 32.5, 30.6, 25.8, 24.5, 23.3, 18.0, −4.0, −5.0; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{35}O_2Si$ 323.2406, found 323.2400.

*6-Methylene-1,2,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]-annulen-8-yl)oxy)silane (**36**).* To a solution of **35** (9.66 g, 30 mmol) and pyridine (24 mL) in CH_2Cl_2 (500 mL) at −78 °C was added Tf_2O (12.3 mL, 75 mmol). The reaction mixture was allowed to warm to 0 °C over 15 min and treated with isopropyl alcohol (3.6 mL, 45 mmol). The resulting solution was stirred at 25 °C for 15 min and then quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether (100 mL × 3). The combined organic extracts were washed with saturated aqueous NH_4Cl solution, water, and brine, dried over $MgSO_4$, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 99:1) of the residue gave a colorless oil (8.6 g, 28.2 mmol, 84%) as the product. **36**: ^{1}H NMR (400 MHz, $CDCl_3$ δ 5.71−5.53 (m, 1H), 5.46 (d, J = 9.8 Hz, 1H), 4.95 (s, 1H), 4.92 (s, 1H), 3.76 (ddd, J = 10.8, 5.8, 3.0 Hz, 1H), 2.50 (s, 1H), 2.38−2.15 (m, 2H), 2.07−2.01 (m, 2H), 1.89−1.62 (m, 3H), 1.58−1.44 (m, 4H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 134.9, 126.7, 107.1, 71.2, 50.8, 46.0, 43.8, 40.4, 40.1, 36.1, 27.3, 26.3, 25.8, 18.1, −4.6, −4.7; IR (neat, cm^{-1}) 2963, 2939, 2866, 1680, 1472, 1253, 1094, 878, 832, 777; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{33}OSi$ 305.2301, found 305.2304.

*6-Methylene-1,2,5,6,7,8,9,9a-octahydro-4a,7-methanobenzo[7]-annulen-8-ol (**37**).* To a solution of **36** (6.08 g, 20 mmol) in THF (50 mL) and MeOH (5 mL) was added a 2 N HCl aqueous solution (50 mL) at room temperature. The reaction mixture was stirred for 1 h and then quenched by saturated aqueous $NaHCO_3$ solution. After being diluted with diethyl ether (100 mL), the aqueous layer was extracted with diethyl ether (100 mL × 3) and the combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 9:1) of the residue gave a white solid (3.80 g, 20 mmol, 100%) as the product. **37**: mp = 59.7−60.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (td, J = 9.4, 3.4 Hz, 1H), 5.46 (td, J = 9.8, 1.8 Hz, 1H), 4.95 (s, 2H), 3.72 (s, 1H), 2.60 (s, 1H), 2.38−2.18 (m, 2H), 2.07−2.04 (m, 2H), 1.77−1.67 (m, 4H), 1.66−1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 134.4, 126.9, 106.5, 70.0, 50.6, 45.8, 43.7, 40.4, 39.8, 36.1, 26.9, 26.2; IR (neat, cm^{-1}) 3403, 2927, 2866, 1652, 1451, 1427, 1046, 881, 698; HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{19}O$ 191.1436, found 191.1439.

*6-Methylene-1,2,6,7,9,9a-hexahydro-4a,7-methanobenzo[7]-annulen-8(5H)-one (**12**).* To a stirred solution of **37** (1.90 g, 10 mmol) in CH_2Cl_2 (100 mL) at room temperature were added $NaHCO_3$ (2.52 g, 30 mmol) and Dess-Martin periodinane (6.39 g, 15 mmol). The reaction mixture was stirred at room temperature for 30 min, and then the solution was quenched with a saturated $Na_2S_2O_3$ aqueous solution (20 mL). The aqueous layer was extracted by diethyl ether (50 mL × 3), and the combined organic extracts were washed with saturated a $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 20:1) of the residue gave a colorless oil (1.69 g, 9.0 mmol, 90%) as the product.

*8-((tert-Butyldimethylsilyl)oxy)-6-methyleneoctahydro-4a,7-methanobenzo[7]annulen-4(1H)-one (**38**).* To a stirred solution of **35** (6.44 g, 20 mmol) in CH_2Cl_2 (200 mL) at room temperature were added $NaHCO_3$ (5.04 g, 60 mmol) and Dess-Martin periodinane (12.7 g, 30 mmol). The reaction mixture was stirred at room temperature for 30 min and then quenched with a saturated $Na_2S_2O_3$ aqueous solution (40 mL). The aqueous layer was extracted by diethyl ether (50 mL × 2), and the combined organic extracts were washed with a saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 20:1) of the residue gave a white solid (5.76 g, 18 mmol, 90%) as the product. **38**: mp = 73.0−73.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (s, 2H), 3.88 (ddd, J = 10.6, 5.8, 3.0 Hz, 1H), 3.09 (td, J = 17.5, 2.7 Hz, 1H), 2.62 (dd, J = 5.1, 2.8 Hz, 1H), 2.48−2.23 (m, 2H), 2.16−1.87 (m, 5H), 1.76−1.52 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 147.3, 107.9, 70.1, 57.3, 51.2, 44.4, 39.0, 37.7, 36.6, 35.2, 28.8, 26.2, 25.7, 18.1, −4.6, −4.7; IR (neat, cm^{-1}) 2945, 2866, 1710, 1658, 1472, 1256, 1131, 1106, 1079, 875, 838, 780; HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{34}O_2Si$ 322.2328, found 322.2333.

*8-((tert-Butyldimethylsilyl)oxy)-6-methylene-5,6,7,8,9,9a-hexahydro-4a,7-methanobenzo[7]annulen-4(1H)-one (**29**) from **38**.* To a solution of diisopropylamine (3.29 mL, 23.4 mmol) in THF (24 mL) was added dropwise a solution of *n*-butyllithium (a 2.5 M solution in hexanes, 9 mL, 22.5 mmol) at −78 °C under argon. After being stirred for 30 min at −78 °C, this solution was added dropwise to a solution of **38** (18 mmol) in THF (36 mL) via cannulation. The resulting mixture was stirred at −78 °C for 1 h and then treated with trimethylsilyl chloride (freshly distilled from calcium hydride, 11 mL, 90 mmol). After stirring at −78 °C for another hour, the volatiles were removed under reduced pressure at 0 °C. The residue was then dissolved in CH_3CN (180 mL) and treated with $Pd(OAc)_2$ (4.04 g, 18 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was then filtered and concentrated. Silica gel

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flash column chromatography (hexanes/ethyl acetate = 20:1) of the residue gave a white solid (4.97 g, 15.6 mmol, 87%) as the product.

■ ASSOCIATED CONTENT

Supporting Information

Binding enthalpies of 29 Lewis acids toward styrene and benzaldehyde, total energies and coordinates of optimized minima and transition states, the X-ray structures of compounds **6a** and **6i**, and ^{1}H NMR and ^{13}C NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Alloco, J.; A'BasilioTormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J.; Bartizal, K.; Barrett, J.; Schmatz, D. J.; Becker, W.; Cully, D.; Singh, S. B. *Nature* **2006**, *441*, 358−361.
(2) Wang, J.; Kodali, S.; Lee, S. H.; Galgoci, A.; Painter, R.; Dorso, K.; Racine, F.; Motyl, M.; Hernandez, L.; Tinney, E.; Colletti, S.; Herath, K.; Cummings, R.; Salazar, O.; Gonzalez, I.; Basilio, A.; Vicente, F.; Genilloud, O.; Pelaez, F.; Jayasuriya, H.; Young, K.; Cully, D.; Singh, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 7612−7616.
(3) Herath, K.; Attygalle, A. B.; Singh, S. B. *J. Am. Chem. Soc.* **2007**, *129*, 15422−15423.
(4) Smanski, M. J.; Yu, Z.; Casper, J.; Lin, S.; Peterson, R. M.; Chen, Y.; Wendt-Pienkowski, E.; Rajski, S. R.; Shen, B. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *108*, 13498−13503.
(5) Häbich, D.; von Nussbaum, F. *ChemMedChem* **2006**, *1*, 951−954.
(6) Brown, E. D. *Nature* **2006**, *441*, 293−294.
(7) Pearson, H. *Nature* **2006**, *441*, 260−261.
(8) Brinster, S.; Lamberet, G.; Staels, B.; Trieu-Cuot, P.; Gruss, A.; Poyart, C. *Nature* **2009**, *458*, 83−86.
(9) Martens, E.; Demain, A. L. *J. Antibiot.* **2011**, *64*, 705−710.
(10) Brinster, S.; Lamberet, G.; Staels, B.; Trieu-Cuot, P.; Gruss, A.; Poyart, C. *Nature* **2009**, *458*, 83−86.
(11) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2548−2555.
(12) Manallack, D. T.; Crosby, I. T.; Khakham, Y.; Capuano, B. *Curr. Med. Chem.* **2008**, *15*, 705−710.
(13) Yao, Y.-S.; Yao, Z.-J. *Chin. J. Org. Chem.* **2008**, *28*, 1553−1560.
(14) Harsh, P.; O'Doherty, G. A. *Chemtracts* **2009**, *22*, 31−40.
(15) Lu, X.; You, Q. *Curr. Med. Chem.* **2010**, *17*, 1139−1155.
(16) Palanichamy, K.; Kaliappan, K. P. *Chem.—Asian J.* **2010**, *5*, 668−703.
(17) Nicolaou, K. C.; Chen, J. S. D.; Edmonds, J.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 660−719.
(18) Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290−2303.
(19) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086−7090.
(20) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942−3945.
(21) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825−1828.
(22) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417−2419.
(23) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922−1923.
(24) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534−9535.
(25) Ghosh, A. K.; Kai, X. *Org. Lett.* **2007**, *9*, 4013−4016.
(26) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8074−8075.
(27) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921−4923.
(28) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Montero, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4712−4714.
(29) Nicolaou, K. C.; Tang, Y.; Wang, J.; Stepan, A. F.; Li, A.; Montero, A. *J. Am. Chem. Soc.* **2007**, *129*, 14850−14851.
(30) Nicolaou, K. C.; Pappo, D.; Tsang, K. Y.; Gibe, R.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 944−946.
(31) Kim, C. H.; Jang, K.; Choi, P. S.; Chung, Y. Y. K.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4009−4011.
(32) Matsuo, J.; Takeuchi, K.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 4049−4052.
(33) Yeung, Y.-Y.; Corey, E. J. *Org. Lett.* **2008**, *10*, 3877−3878.
(34) Nicolaou, K. C.; Stepan, A. F.; Lister, T.; Li, A.; Montero, A.; Tria, G. S.; Turner, C. I.; Tang, Y.; Wang, J. R.; Denton, M.; Edmonds, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 13110−13119.
(35) Yun, S. Y.; Zheng, J.-C.; Lee, D. *J. Am. Chem. Soc.* **2009**, *131*, 8413−8415.
(36) Ghosh, A. K.; Xi, K. *J. Org. Chem.* **2009**, *74*, 1163−1170.
(37) Nicolaou, K. C.; Li, A.; Ellery, S. P.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6293−6295.
(38) McGrath, N. A.; Bartlett, E. S.; Sittihan, S.; Njardarson, J. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8543−8546.
(39) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 16905−16918.
(40) Shen, H. C.; Ding, F.-X.; Singh, S. B.; Parthasarathy, G.; Soisson, S. M.; Ha, S. N.; Chen, X.; Kodali, S.; Wang, J.; Dorso, K.; Tata, J. R.; Hammond, M. L.; MacCoss, M.; Colletti, S. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1623−1627.
(41) Wang, J.; Lee, V.; Sintim, H. O. *Chem.—Eur. J.* **2009**, *15*, 2747−2750.
(42) Jang, K. P.; Kim, C. H.; Na, S. W.; Kim, H.; Kang, H.; Lee, E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4601−4602.
(43) Jang, K. P.; Kim, C. H.; Na, S. W.; Jang, D. S.; Kang, H.; Lee, E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2156−2158.
(44) Tiefenbacher, K.; Trondlin, L.; Mulzer, J.; Pfaltz, A. *Tetrahedron* **2010**, *66*, 6508−6513.
(45) Eey, S. T.-C.; Lear, M. J. *Org. Lett.* **2010**, *12*, 5510−5513.
(46) Magnus, P.; Rivera, H.; Lynch, V. *Org. Lett.* **2010**, *12*, 5677−5679.
(47) Oblak, E. Z.; Wright, D. L. *Org. Lett.* **2011**, *13*, 2263−2265.
(48) Wang, J.; Sintim, H. O. *Chem.—Eur. J.* **2011**, *17*, 3352−3357.
(49) Heretsch, P.; Giannis, A. *Synthesis* **2007**, 2614−2616.
(50) Maras, N.; Anderluh, P. S.; Urleb, U.; Kocevar, M. *Synlett* **2009**, 437−440.
(51) McNulty, J.; Nair, J. J.; Capretta, A. *Tetrahedron Lett.* **2009**, *50*, 4087−4091.
(52) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1780−1783.
(53) Hayashida, J.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4373−4376.

(54) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2548−2555.
(55) Yun, S. Y.; Zheng, J.-C.; Lee, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 6201−6203.
(56) Waalboer, D. C. J.; Schaapman, M. C.; van Delft, F. L.; Rutjes, F. P. J. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6576−6578.
(57) Nicolaou, K. C.; Toh, Q.-Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 11292−11293.
(58) Austin, K. A. B.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2008**, *10*, 4465−4468.
(59) Varseev, G. N.; Maier, M. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3685−3688.
(60) Tiefenbacher, K.; Mulzer, J. *J. Org. Chem.* **2009**, *74*, 2937−2941.
(61) Barykina, O. V.; Rossi, K.; Rybak, L. M. J.; Snider, B. B. *Org. Lett.* **2009**, *11*, 5334−5337.
(62) Ghosh, A. K.; Xi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5372−5375.
(63) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. *J. Am. Chem. Soc.* **2009**, *131*, 15909−15917.
(64) Hirai, S.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 5076−5079.
(65) Singh, V.; Sahu, B. C.; Bansal, V.; Mobin, S. M. *Org. Biomol. Chem.* **2010**, *8*, 4472−4481.
(66) Li, P.; Yamamoto, H. *Chem. Commun.* **2010**, *46*, 6294−6295.
(67) Waalboer, D. C. J.; Leenders, S. H. A. M.; Schuelin-Casonato, T.; van Delft, F. L.; Rutjes, F. P. J. T. *Chem.—Eur. J.* **2010**, *16*, 11233−11236.
(68) Tiefenbacher, K.; Gollner, A.; Mulzer, J. *Chem.—Eur. J.* **2010**, *16*, 9616−9622.
(69) Leung, G. Y. C.; Li, H.; Toh, Q.-Y.; Ng, A. M.-Y.; Sum, R. J.; Bandow, J. E.; Chen, D. Y.-K. *Eur. J. Org. Chem.* **2011**, 183−196.
(70) Hirai, S.; Nakada, M. *Tetrahedron* **2011**, *67*, 518−530.
(71) Yoshimitsu, T.; Nojima, S.; Hashimoto, M.; Tanaka, T. *Org. Lett.* **2011**, *13*, 3698−3701.
(72) Palanichamy, K. A.; Subrahmanyam, V.; Kaliappan, K. P. *Org. Biomol. Chem.* **2011**, *9*, 7877−7886.
(73) Babu, S. A. *Synlett* **2002**, 531−532.
(74) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Curr. Org. Chem.* **2003**, *7*, 1661−1689.
(75) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817−7831.
(76) Baba, A.; Yasuda, M.; Nishimoto, Y.; Saito, T.; Onishi, Y. *Pure Appl. Chem.* **2008**, *80*, 845−854.
(77) Itoh, Y.; Tsuji, H.; Yamagata, K.-i.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161−17167.
(78) Peng, W.; Lee, C.-S. *Synlett* **2008**, 142−146.
(79) Li, W.; Liu, X.; Zhou, X.; Lee, C.-S. *Org. Lett.* **2010**, *12*, 548−551.
(80) Han, Y.; Zhu, L.; Lee, C.-S. *Org. Lett.* **2011**, *13*, 588−591.
(81) Huang, S.; Du, G.; Lee, C.-S. *J. Org. Chem.* **2011**, *76*, 6534−6541.
(82) Liu, X.; Lee, C.-S. *Org. Lett.* **2012**, *14*, 2886−2889.
(83) Zhu, L.; Han, Y.; Du, G.; Lee, C.-S. *Org. Lett.* **2013**, *15*, 524−527.
(84) Qasseem, M. A.; Rogers, N. A. J.; Othman, A. A. *Tetrahedron* **1968**, *24*, 4535−4542.
(85) Corey, E. J.; Liu, K. *Tetrahedron Lett.* **1997**, *38*, 7491−7494.
(86) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916−4925.
(87) The NMR data are available in the Supporting Information.
(88) The crystals of **6a**, **6b**, and **6i** were obtained by recrystallization from *n*-hexane. CCDC-909564 (**6a**), CCDC-950106 (**6b**), and CCDC-909565 (**6i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(89) Wang, T.; Liang, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 9343−9353.
(90) Imamura, K.-i.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4081−4084.
(91) Chen, S. L.; Zhang, H. P.; Wang, L. Q.; Bao, G. H.; Qin, G. W. *J. Nat. Prod.* **2004**, *67*, 1903−1906.
(92) Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 813−814.
(93) Liu, A.; Liu, Z. Z.; Zou, Z. M.; Chen, S. Z.; Xu, L. Z.; Yang, S. L. *Tetrahedron* **2004**, *60*, 3689−3694.
(94) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227.
(95) Amate, Y.; Bretón, J. L.; Garcia-Granados, A.; Martinez, A.; Onorato, M. E.; de Buruaga, A. S. *Tetrahedron* **1990**, *46*, 6939−6950.
(96) Reizlman, A.; Zwanenburg, B. *Synthesis* **2000**, 1952−1955.
(97) Xia, W. J.; Li, D. R.; Shi, L.; Tu, Y. Q. *Tetrahedron Lett.* **2002**, *43*, 627−630.
(98) Reitz, A.; Avery, M. A.; Verlander, M. S.; Goodman, M. *J. Org. Chem.* **1981**, *46*, 4859−4863.
(99) Keinan, E.; Peretz, M. *J. Org. Chem.* **1983**, *48*, 5302−5309.
(100) Curzon, E.; Golding, B. T.; Pierpoint, C.; Waters, B. W. *J. Organomet. Chem.* **1984**, *262*, 263−269.
(101) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687−3696.
(102) Pasqua, A. E.; Ferrari, F. D.; Hamman, C.; Liu, Y.; Crawford, J. J.; Marquez, R. *J. Org. Chem.* **2012**, *77*, 6989−6997.
(103) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615−3616.
(104) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.
(105) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.;. Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A.; Farkas, D.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision A.1; Gaussian, Inc.: Wallingford, CT, 2009.
(106) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100.
(107) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(108) Vosko, S. H.; Wilk, L.; Nussair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211.
(109) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(110) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(111) Dunning, T. H. Jr.; Hay, P. J. In *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum: New York, 1976; Vol. 3, pp 1−28.
(112) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270−283.
(113) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284−298.
(114) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299−310.
(115) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081−6090.
(116) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161−4163.
(117) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368.
(118) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154−2161.
(119) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523−5527.
(120) Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829−5835.
(121) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.
(122) Zhang, X. H.; Schwarz, H. *Chem.—Eur. J.* **2010**, *16*, 5882−5888.
(123) Zhang, X. H.; Schwarz, H. *Theor. Chem. Acc.* **2011**, *129*, 389−399.

(124) The basis sets were obtained from the Gaussian Basis Set Library EMSL at https://bse.pnl.gov/bse/portal.
(125) Feller, D. *J. Comput. Chem.* **1996**, *17*, 1571−1586.
(126) Schuchardt, K. L.; Didier, B. T.; Elsethagen, T.; Sun, L.; Gurumoorthi, V.; Chase, J.; Li, J.; Windus, T. L. *J. Chem. Inf. Model* **2007**, *47*, 1045−1052.
(127) Metz, B.; Stoll, H.; Dolg, M. *J. Chem. Phys.* **2000**, *113*, 2563−2569.