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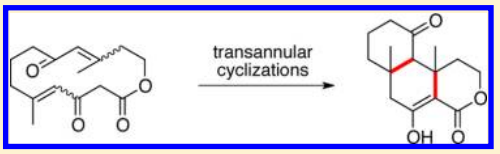
Stereochemical Study of a Transannular Michael Reaction Cascade

Haoran Xue, Peddabuddi Gopal, and Jiong Yang*

Department of Chemistry, Texas A&M University, College Station, Texas 77842, United States

Supporting Information

ABSTRACT: We systematically explored a transannular Michael reaction cascade for stereoselective synthesis of polycyclic systems. Both *E,Z*- and *E,E*-1,7-bis-enones in the form of 14-membered macrocyclic lactones underwent transannular cyclization to give polycyclic products with high efficiency and excellent diastereoselectivity. In contrast, *Z,E*- and *Z,Z*-macrocyclic lactones did not cyclize under similar reaction conditions. Our study revealed similarities and subtle stereochemical differences between this transannular cyclization process and transannular Diels–Alder reactions. An acyl ketene approach was developed for efficient synthesis of macrocyclic lactones. This investigation also illuminated the scope and limitation of macrocyclization by intramolecular Reformatsky reaction to prepare macrocyclic lactones.



INTRODUCTION

Polycyclic molecular frameworks are frequently encountered in natural and unnatural organic compounds that are biomedically relevant. While a number of strategies exist for synthesis of such structural motifs, the transannular approach, which involves cyclization of reaction centers that are tethered as part of a ring system, is particularly effective.[1] This is in part due to entropic activation arising from the macrocyclic environment which brings reaction centers into close proximity and enables reactions that are otherwise difficult under inter- or acyclic intramolecular settings. In addition, macrocycles with unsaturations and ring-substitutions are known to adapt well-defined conformations which form the basis of "macrocyclic stereocontrol".[2] Thus, it is not surprising that transannular cyclization of macrocycles often proceeds with high efficiency and spectacular selectivity. Indeed, it constitutes one of the most powerful approaches for synthesis of stereochemically complex polycyclic structures.

Synthetic application of transannular cyclizations requires that stereoselectivity of the annulation processes be predictable. The macrocyclic substrates also need to be readily accessible. However, except for transannular Diels–Alder reactions and SmI_2-mediated ketone–olefin couplings,[3,4] transannular reactions were mostly studied in isolated examples as part of general synthetic method development while systematic investigations of such processes are rare. Our interests in synthesis and biological evaluation of complex polycyclic marine alkaloids of the zoanthamine family (Figure 1),[5−7] such as zoanthamine (**1**), norzoanthamine (**2**), zoanthenol (**3**), and 28-deoxyzoanthenamine (**4**), led us to explore the feasibility of preparing their highly functionalized and stereochemically complex ABC ring system by a transannular Michael reaction cascade.[8] This reaction cascade could be traced to synthesis of bicyclo[2.2.2]octanes by sequential Michael reactions of cross-conjugated dienolates of cyclohexenones and activated alkenes (Scheme 1).[9] Synthetic methods and complex polycyclic natural product syntheses based on this reaction cascade have been reported.[10] In 2007, Evans and co-workers described an elegant application of the Michael reaction cascade in a transannular setting for the total synthesis of salvinorin A.[11] However, no further investigation of this transformation has been reported. Herein we report our systematic investigation of transannular cyclization of macrocyclic 1,7-bis-enones in the form of 14-membered macrocyclic lactones to give angular 6–6–6 tricyclic ring systems, structural motifs common to polycyclic terpenoids and other natural

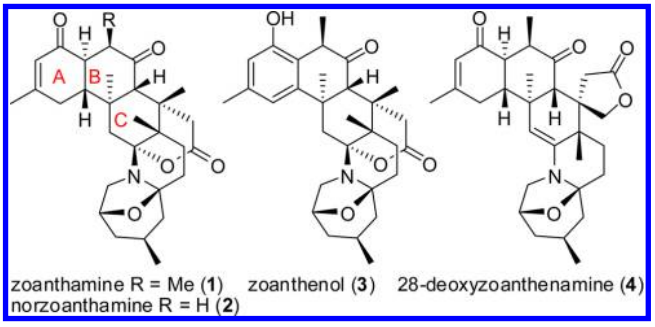
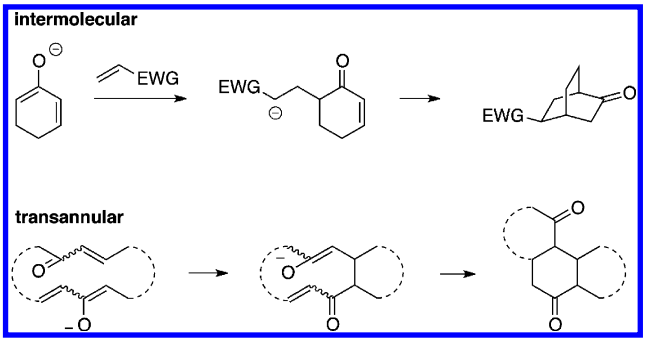


Figure 1. Some zoanthamine alkaloids.

Scheme 1. Michael Reaction Cascade



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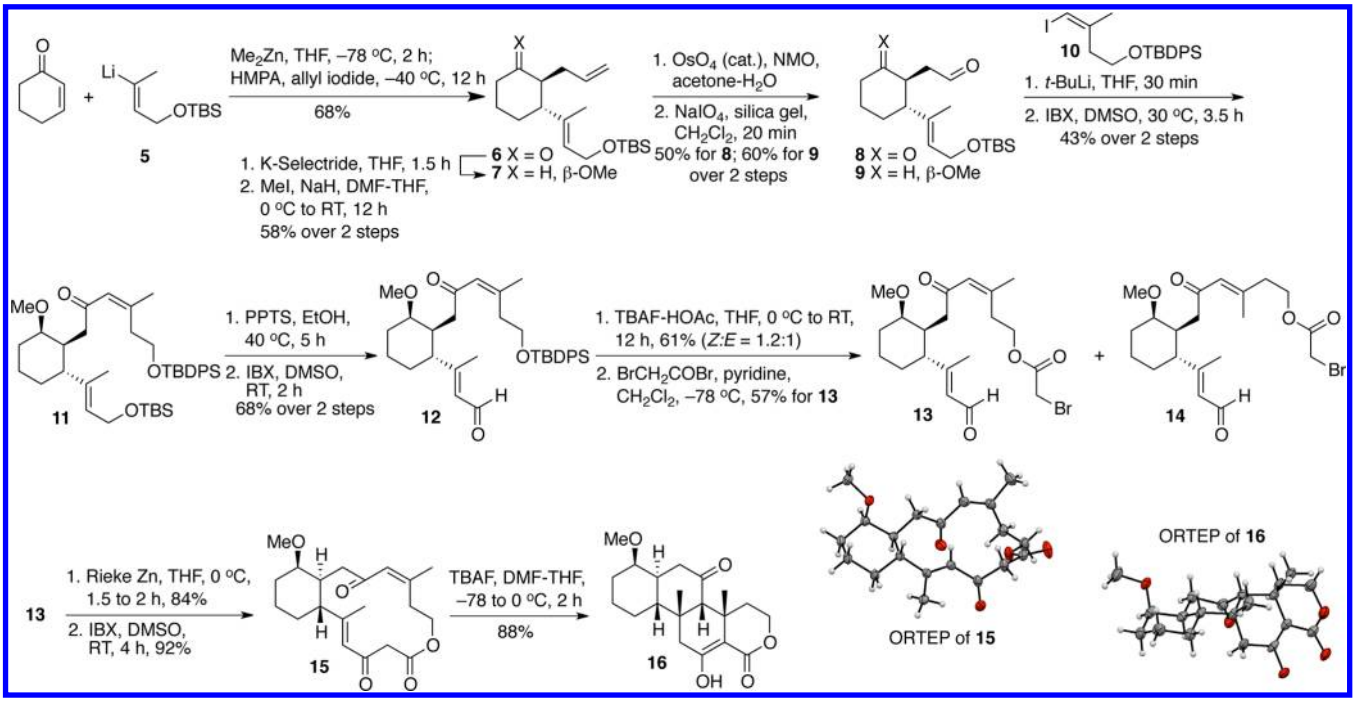
Scheme 2. Synthesis of *E,Z*-Macrocyclic Lactone 15 and Its Transannular Michael Reaction Cascade



products. This study included developing approaches for rapid synthesis of the macrocyclic bis-enone substrates, elucidating the stereochemical courses and other nuances of their transannular cyclization, and comparison of stereoselectivity between transannular Michael reaction cascades and the corresponding Diels–Alder reactions.

RESULTS AND DISCUSSION

An Intramolecular Reformatsky Approach to *E,Z*-Macrocyclic Lactone 15 and Its Transannular Michael Reaction Cascade. Since two enones are necessary for the transannular Michael reaction cascade, four geometrically isomeric macrocyclic substrates are possible. In connection with our synthetic study of zoanthamines, we initiated our investigation by targeting macrocyclic lactone **15** as a pilot substrate to evaluate the efficiency and stereoselectivity of transannular cyclization of macrocyclic *E,Z*-bis-enones (Scheme 2). The synthesis commenced from three-component coupling of cyclohexenone (a mimick of the A ring of zoanthamines), vinyllithium **5**,[12] and allyl iodide.[13] Initial efforts for such a transformation by conjugate addition of the organocopper reagent generated in situ from **5** with cyclohexenone, followed by trapping the enolate intermediate (in situ formed or regenerated from a trimethylsilyl enol ether intermediate) with allyl iodide, were unsuccessful. However, the desired transformation occurred under Noyori conditions by reaction of cyclohexenone with **5** in the presence of Me_2Zn and trapping the zinc enolate intermediate with allyl iodide to give cyclohexanone **6**.[14] The carbonyl group of **6** was reduced with K-Selectride stereoselectively, and the resulting β-hydroxyl group was alkylated with MeI to give **7**. Aldehyde **9** was obtained through selective dihydroxylation of the terminal alkene of **7** and oxidative cleavage of the vicinal diol thus formed with $NaIO_4$. The coupling of **9** and vinyl iodide **10** was effected under Barbier conditions using *t*-BuLi.[15] This was followed by oxidation of the resulting diastereomeric alcohols with IBX to give **11**. Interestingly, similar Barbier coupling of **10** and **8**, in which the cyclohexanone carbonyl group was still in place, only led to reductive dehalogenation of **10** and recovery of **8**.

Further manipulation of **11** involved removal of the *tert*-butyldimethylsilyl protecting group under acidic conditions with PPTS and oxidation of the free hydroxyl group with IBX. The aldehyde thus formed (i.e., **12**) was again desilylated with TBAF and acylated with bromoacetyl bromide to deliver **13** and **14** due to TBAF-mediated isomerization of the *cis*-enone alkene. This provided convenient access of intermediates necessary for synthesis of both *E,Z*- and *E,E*-macrocyclic lactones. Various protocols were explored for macrocyclization of **13** by intramolecular Reformatsky reaction.[16] The most efficient was by slow addition of **13** to a preformed suspension of Rieke Zn in THF.[17] The macrocycle was formed as an inconsequential diastereomeric mixture of β-hydroxyl esters which were oxidized with IBX to give *E,Z*-macrocyclic lactone **15**. The transannular Michael reactions of **15** were initiated by treatment with TBAF in THF–DMF (1:1) to give tetracycle **16** as a single diastereomeric product in 88% yield. Its stereochemical structure was determined using 1D and 2D NMR spectra. The β-keto ester moiety of **15** was found to mostly exist in the keto form, while the enol form predominated in **16**. Other basic reaction conditions, such as NaOMe–DMF and K_2CO_3–DMSO, proved to be equally effective for stereoselective transannular cyclization of **15**.

Both **15** and **16** were crystalline, which allowed X-ray diffraction structural analyses (Scheme 2). The macrocycle of **15** was found to adapt a conformation in which both of the activated alkenes oriented perpendicular to the plane defined by the macrocycle to avoid noncovalent transannular interactions. However, this ground state conformation was clearly different from the one that determined the stereochemical outcome of the reaction since the two *syn*- angular methyl groups of **16** oriented *anti*- in this conformer of **15**.

Control Experiment. We designed β-keto ester **17** as a control substrate to qualitatively evaluate entropic contribution

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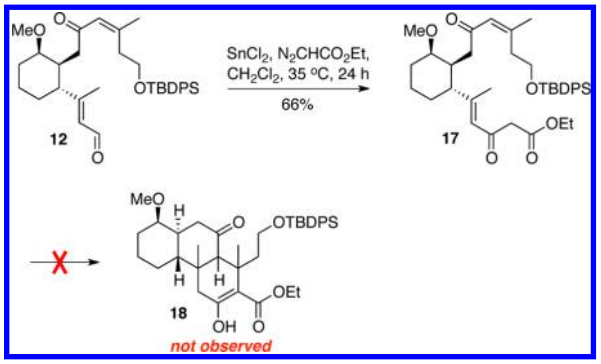
by the macrocyclic environment of **15** to the cyclization reaction. It was prepared by $SnCl_2$-catalyzed Roskamp reaction of **12** with ethyl diazoacetate.[18] In contrast to the facile transannular cyclization of **15**, the acyclic intramolecular Michael reaction cascade of **17** was not observed when it was treated with TBAF at room temperature while elevated temperature led to substrate decomposition only (Scheme 3).

Scheme 3. Control Experiment for Acyclic Intramolecular Michael Reaction Cascade with 17

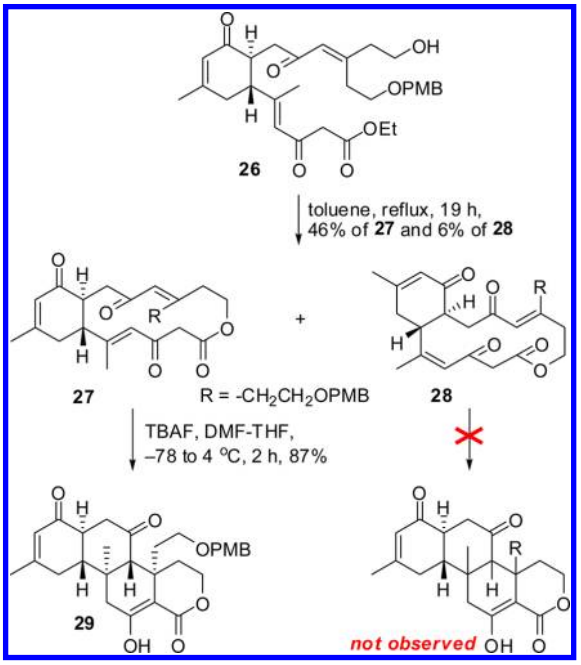


Other basic reaction conditions proved to be ineffective for initiating the transannular cyclization as well. This control experiment demonstrated the macrocycle to be a crucial structural element that enabled the Michael reaction cascade.

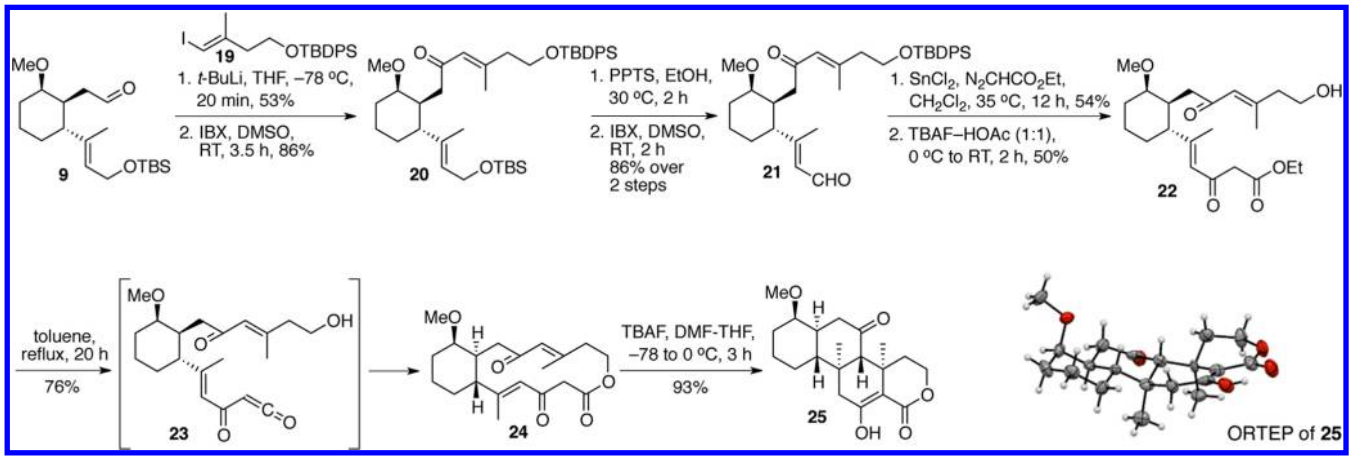
Acyl Ketene Approach to *E,E*-Macrocyclic Lactone 24 and Its Transannular Michael Reaction Cascade. We envisioned aldehyde **14** to be a convenient point of entry to *E,E*-macrocyclic lactone **24**. To our surprise, while intramolecular Reformatsky reaction was effective for macrocyclization of **13**, attempts for preparing the corresponding *E,E*-macrocycle by intramolecular Reformatsky cyclization of **14** under similar conditions led to reductive debromination product only (not shown). This prompted us to develop an acyl ketene approach to *E,E*-macrocyclic lactones. It started from *t*-BuLi-mediated Barbier coupling of **9** and vinyl iodide **19**,[19] which was followed by oxidation of the allylic alcohols thus formed with IBX to give **20** (Scheme 4). Removal of the *tert*-butyldimethylsilyl protecting group of **20** by PPTS followed by oxidation with IBX gave enal **21**, which was subjected to Roskamp reaction and TBAF-mediated desilylation to give **22**. In contrast to that observed for **12**, no isomerization of the *E*-enone alkene of **22** occurred. As we had anticipated, cyclization of **22** went smoothly through the intermediacy of acyl ketene **23**, transiently formed upon refluxing a dilute solution of **22** in toluene,[20] to give *E,E*-macrocyclic lactone **24**. Treatment of **24** with TBAF led to smooth transannular cyclization to give **25** as a single diastereomeric product. Its stereochemical structure was determined by 1D and 2D NMR spectra and verified by X-ray crystallography. The *β*-keto ester moiety of **24** was found to exist in the keto form while the enol form predominated in **25**.

Preparation of *Z,E*-Macrocycles and Examination of Their Transannular Michael Reaction Cascade. We previously reported preparation of *E,E*-macrocyclic lactone **27** through intramolecular acylation of the acyl ketenes generated from **26** (Scheme 5).[8] Subsequent TBAF-mediated transannular cyclization of **27** proceeded with the same stereoselectivity as *E,E*-macrocyclic lactone **24** to give **29** exclusively. Our reinvestigation of macrocyclization of **26** at a preparative scale showed that *Z,E*-macrocyclic lactone **28** was also formed

Scheme 5. Formation of 28 and Examination of Its Transannular Michael Reaction Cascade



Scheme 4. Synthesis of the *E,E*-Macrocycle 24 and Its Transannular Michael Reaction Cascade



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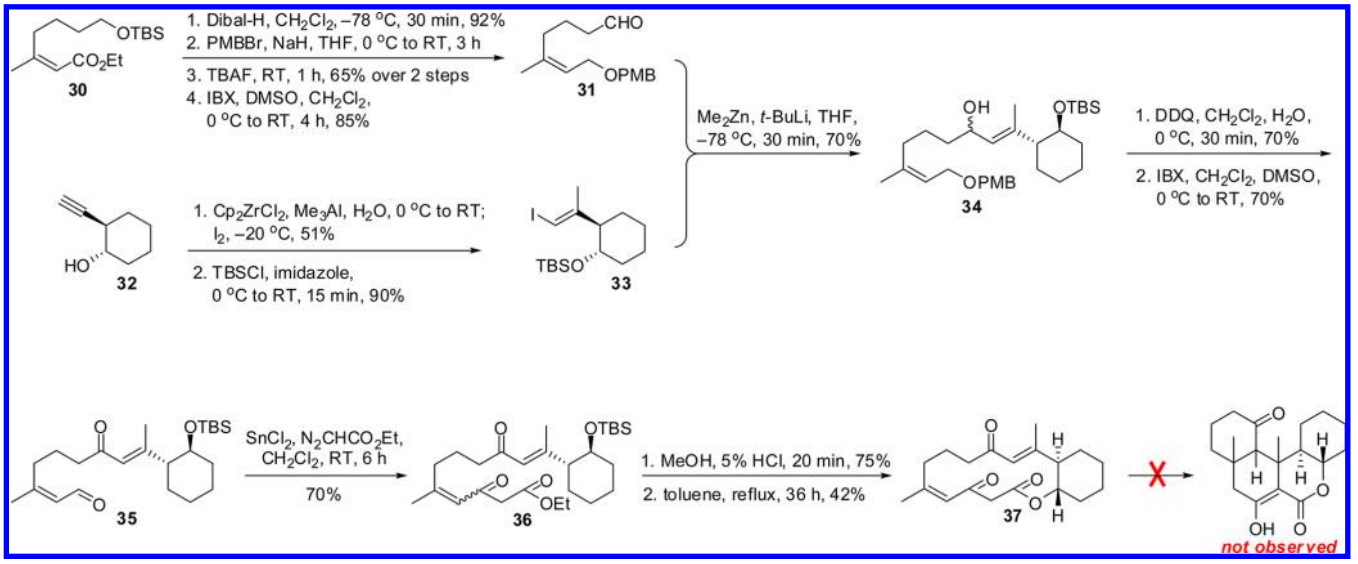
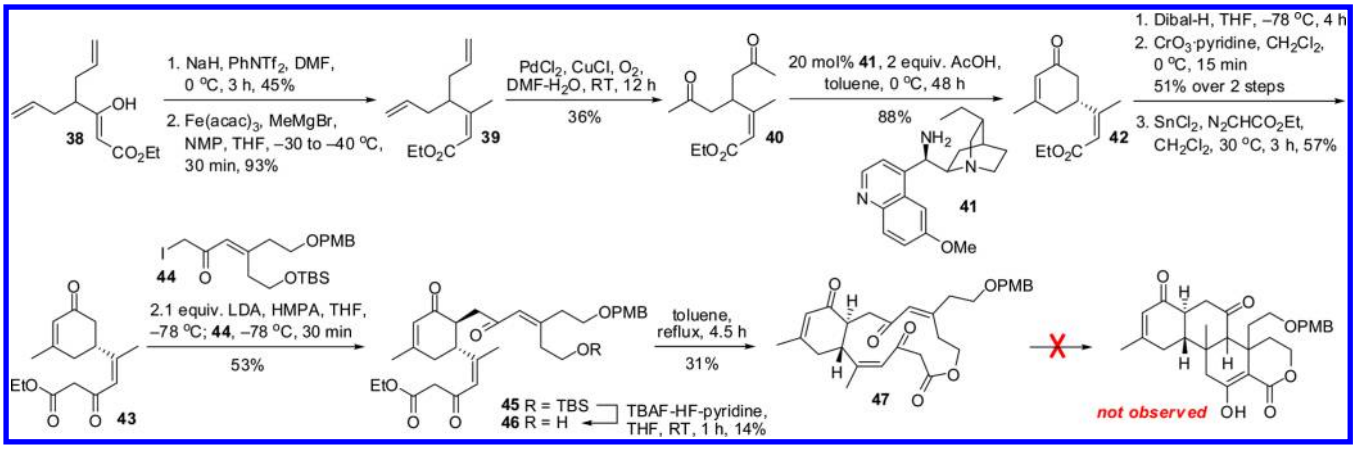
Scheme 6. Preparation of 37 and Examination of Its Transannular Michael Reaction Cascade



Scheme 7. Preparation of *Z,Z*-Macrocyclic Lactone 47 and Testing the Transannular Michael Reaction Cascade



as a minor product due to alkene isomerization. It was used as a model substrate to examine transannular cyclization of macrocyclic *Z,E*-bis-enones. To our surprise, while the *E,Z*- and *E,E*-macrocyclic lactones readily underwent transannular cyclizations upon treatment with TBAF to give single diastereomeric products, the *Z,E*-macrocyclic lactone **28** remained intact under similar reaction conditions. Attempts for initiating transannular cyclization of **28** at elevated temperatures led to substrate decomposition and no transannular cyclization products were formed. Other basic reaction conditions proved to be ineffective as well.

To further evaluate the reactivity of macrocyclic *Z,E*- bis-enones for transannular cyclization, we prepared lactone **37** in which cyclohexane fused with the macrocycle differentially from that in **28** (Scheme 6). The synthesis of **37** commenced with reduction of **30** with DIBAL-H and PMB-etherification of the allylic alcohol thus formed.[21] The resulting PMB ether was subjected to desilylation and oxidation with IBX to give aldehyde **31**. Vinyl iodide **33** was prepared by carbometalation of hydroxyl alkyne **32** with Cp_2ZrCl_2–Me_3Al followed by iodinolysis and *tert*-butyldimethylsilylation of the free hydroxyl group.[22,23] In the presence of Me_2Zn, the coupling of aldehyde **31** and vinyl iodide **33** went smoothly with *t*-BuLi under Barbier conditions to give **34**. Removal of the PMB protecting group of **34** with DDQ followed by oxidation of the resulting diol with IBX gave aldehyde **35**, which was subjected to Roskamp reaction to afford a mixture of *E*- and *Z*- isomeric (1.2:1) *β*-keto esters **36** due to isomerization of the enal alkene. Macrocyclic lactone **37** was formed upon TBAF-mediated desilylation of **36** and intramolecular acylation through the intermediacy of transient acyl ketenes formed in refluxing toluene.[24] Again, attempts to initiate transannular cyclization of *Z,E*-macrocyclic lactone **37** were not successful. While it was recovered intact upon treatment with TBAF at room temperature, extensive decomposition of **37** was observed at elevated temperatures.

Preparation of *Z,Z*-Macrocyclic Lactone 47 and Examination of Its Transannular Michael Reaction Cascade. To fully explore this transannular cyclization process, we synthesized *Z,Z*-macrocyclic lactone **47** as shown in Scheme 7. This involved converting *β*-keto ester **38**[25] to *Z*-enoate **39** via *E*-selective enol triflation with $PhNTf_2$–NaH and $Fe(acac)_3$-catalyzed methylation of the enol triflate thus formed with MeMgBr.[26] Simultaneous Wacker oxidation of both of the terminal alkenes of **39** gave 2,6-heptadione **40**, which was subjected to the intramolecular aldolization under the catalysis of primary amine **41** to give cyclohexenone **42**.[27] A procedure that consisted of DIBAL-H reduction, oxidation with Collins

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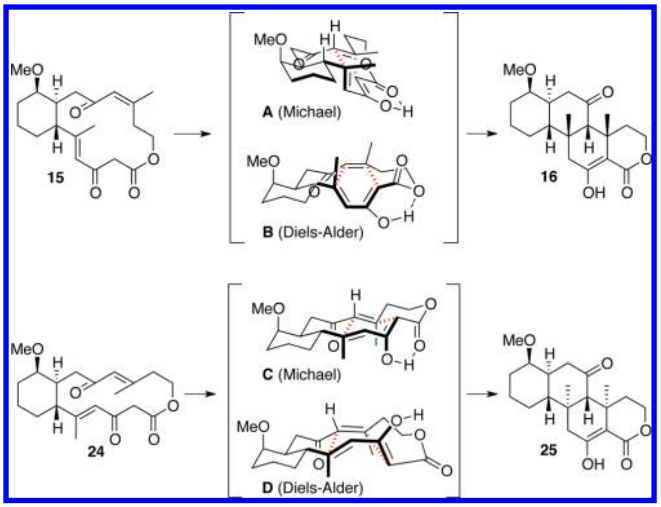
reagent,[28] and Roskamp reaction served to convert **42** to β-keto ester **43** and its *E*-isomer (3:1, not shown) due to isomerization of the enal alkene. Regioselective coupling of **44**[29] with the dienolate of **43** went smoothly to give **45** in 53% yield. Macrocyclic lactone **47** was obtained upon buffered desilylation of **45** with TBAF-HF-py followed by acyl ketene-mediated macrocyclization of thus formed **46** in refluxing toluene.[30] Despite our efforts, transannular cyclization of *Z,Z*-macrocyclic lactone **47** could not be initiated under TBAF or other basic reaction conditions. Instead, the macrocyclic lactone was either recovered under mild reaction conditions (such as TBAF at room temperature) or decomposed without cyclization at elevated temperature.

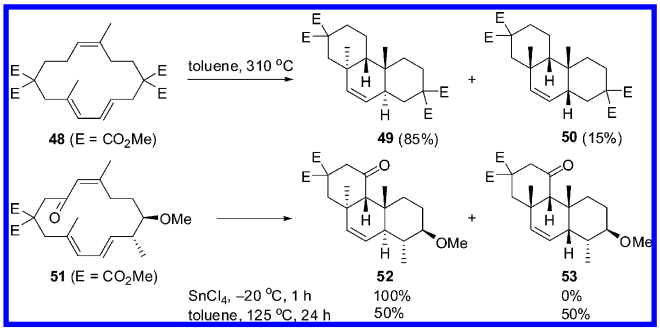
Some Mechanistic Considerations. The stereochemical outcome of transannular cyclization of *E,Z*- macrocyclic lactone **15** could be rationalized using transition state **A** in which all incipient six-membered rings adapt a chairlike conformation (Scheme 8). Similarly, transannular Michael reaction cascade of

Scheme 8. Stereochemical Models for Transannular Cyclization of 15 and 24



E,E-macrocycle **24** through all-chairlike transition state **C** would lead to **25** stereoselectively. However, chair−chair−boat−chair transition states **B** and **D** could also be envisioned for **15** and **24** through which stereoselective transannular Diels−Alder reactions would similarly lead to formation of **16** and **25**, respectively. These two mechanistic possibilities could not be readily distinguished because the mechanistically relevant stereochemical information of the initially formed β-keto ester moieties of **16** and **25** was lost to tautomerization. However, informative indirect comparison could be made between the stereochemical outcome of transannular cyclization of macrocyclic 1,7-bis-enones and that of transannular Diels−Alder reactions reported by Deslongchamp and coworkers.[3] Similar reactivity patterns were observed for these two transannular cyclization processes. The most notable was the low kinetic barrier associated with transannular Diels−Alder cyclization of *trans-trans-cis* (TTC) and *trans-trans-trans* (TTT) macrocyclic trienes compared with that of other trienes.[31] *E,Z*- and *E,E*-macrocyclic lactones, assuming their β-keto esters adapted the extended *Z*-configuration in their enol forms, also existed in the TTC (for **15**) and TTT (for **24** and **27**) configurations. Our studies demonstrated that both *E,Z*- and *E,E*-macrocyclic lactones underwent smooth transannular cyclization while the *Z,E* and *Z,Z* macrocycles (i.e., **28**, **37**, and **47**) did not cyclize under similar reaction conditions. On the other hand, the stereochemical outcome of these two types of transannular cyclization processes showed interesting discrepancies. Under thermal reaction conditions, TTC triene **48** was reported to undergo transannular Diels−Alder reactions to give predominantly *trans-syn-trans* (TST) product **49** while its *cis-syn-cis* (CSC) isomer **50** was formed as the minor product (Scheme 9).[32] Activated TTC triene **51** was found to undergo

Scheme 9. Transannular Diels−Alder Reactions of *Trans−Trans−Cis* (TTC) Trienes



similar thermal transannular Diels−Alder reactions to give equal amounts of the isomeric TST and CSC products (i.e., **52** and **53**), while only the TST product **52** was obtained under Lewis acid catalysis with $SnCl_4$. Interestingly, transannular cyclization of *E,Z*-macrocyclic lactone **15** gave exclusively a product (i.e., **16**) that could only arise from CSC cyclization if such cyclization proceeded by the Diels−Alder mechanism. Thus, while the mechanistic detail for transannular cyclization of *E,E*- macrocyclic lactones (i.e., **24** and **27**) remains elusive because both mechanistic pathways lead to the same product, the stereochemical outcome for transannular cyclization of *E,Z*-macrocyclic lactone **15** appears to be different from that of transannular Diels−Alder cyclization.

CONCLUSION

We systematically explored a transannular Michael reaction cascade for stereoselective formation of polycycles. Our study demonstrated that *E,Z*- and *E,E*- 1,7-bis-enones in the form of 14-membered macrocyclic lactones underwent smooth transannular Michael reactions to give diastereomeric polycycles with high efficiency and excellent diastereoselectivity. However, *Z,E*- and *Z,Z*- macrocyclic lactones failed to cyclize under similar reaction conditions.[33] In addition to elucidating the scope and limitation of this transannular cyclization process, our study also revealed similarities and differences between this transannular Michael reaction cascade and Diels−Alder reactions. In particular, our study demonstrated that *E,Z*-macrocyclic lactones underwent transannular cyclization to give rise to polycycles not readily available by transannular Diels−Alder approaches. As part of the investigation, the scope and limitation of an intramolecular Reformatsky approach for synthesis of macrocyclic lactones were illuminated. In comparison, the acyl ketene approach, which would furnish the desired β-keto ester moiety without oxidation state adjustment, appeared to be general for synthesis of macrocyclic lactones. Studies to apply the transannular Michael reaction cascade in synthesis of zoanthamines are in progress and will be reported in due course.

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EXPERIMENTAL SECTION

(2*S*,3*R*)-2-Allyl-3-((*E*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-2-yl)cyclohexanone (6). To a stirred solution of *t*-BuLi (1.7 M in heptane) in THF (127 mL) at −78 °C was added vinyl iodide **5** (6.47 g, 20.7 mmol) in THF (40 mL) in 20 min. The solution was kept at the same temperature for 1 h before a solution of Me_2Zn in toluene (2 M, 10.8 mL, 21.7 mmol) was added. The solution was allowed to warm to 0 °C and stirred for 15 min before it was cooled to −78 °C. The solution was treated with 2-cyclohexenone (2.2 mL, 22.8 mmol) dropwise and stirred for 2 h before HMPA (33 mL, 188 mmol) was added. The mixture was stirred for 10 min before allyl iodide (15.5 g, 94 mmol) was added. The mixture was warmed to −40 °C and maintained at this temperature overnight. The reaction mixture was quenched with satd aq NH_4Cl and extracted with ethyl acetate (3 × 60 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4 before it was concentrated *in vacuo*. Purification of the reaction crude by column chromatography gave cyclohexenone **6** (4.55 g, 14.1 mmol, 68%) as light yellow oil: IR (neat, cm^{-1}) 3076, 2928, 2860, 1717; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91−5.71 (m, 1H), 5.37 (t, J = 6.0 Hz, 1H), 5.02−4.86 (m, 2H), 4.21 (d, J = 6.1 Hz, 2H), 2.46−2.36 (m, 2H), 2.32 (m, 1H), 2.28−2.13 (m, 2H), 2.12−1.96 (m, 2H), 1.84−1.71 (m, 2H), 1.71−1.63 (m, 1H), 1.60 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 137.0, 136.4, 127.4, 115.6, 59.9, 53.8, 52.8, 42.1, 31.0, 30.8, 26.1, 25.9, 18.3, 12.5, −5.1; HRMS (ESI) calcd for $C_{19}H_{35}O_2Si^+$ $[M + H]^+$ 323.2406, obsd 323.2414.

(((*E*)-3-((1*R*,2*S*,3*R*)-2-Allyl-3-methoxycyclohexyl)but-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (7). To a solution of cyclohexenone **6** (4.19 g, 13 mmol) in THF (29 mL) was added a solution of K-Selectride in THF (1 M, 14.3 mL, 14.3 mmol) in 15 min. The reaction was stirred at −78 °C for 1.5 h and quenched with 10% aq NaOH (5 mL), 30% H_2O_2 (10 mL) before being warmed to room temperature. The mixture was stirred for another 20 min before it was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography to give alcohol **6S** (3.43 g, 82%) as colorless oil: IR (neat, cm^{-1}) 3500, 2931, 2857; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03−5.63 (m, 1H), 5.53−5.25 (m, 1H), 5.22−4.82 (m, 2H), 4.20 (dd, J = 6.1, 0.7 Hz, 2H), 4.03 (s, 1H), 2.26−2.00 (m, 2H), 1.89 (ddd, J = 13.5, 13.0, 5.8 Hz, 2H), 1.80−1.64 (m, 1H), 1.64−1.58 (m, 2H), 1.58−1.49 (m, 4H), 1.49−1.22 (m, 5H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ138.6, 137.6, 126.2, 115.8, 67.1, 60.1, 46.2, 43.0, 34.4, 33.2, 31.7, 25.9, 19.7, 18.3, 12.6, −5.1; HRMS (ESI) calcd for $C_{19}H_{37}O_2Si^+$ $[M + H]^+$ 325.2563, obsd 325.2576.

To a mixture of alcohol **6S** (1.57 g, 4.6 mmol) and methyl iodide (1.15 mL, 18.5 mmol) in DMF−THF (20 mL−9.2 mL) was added NaH (95%, 0.223 g, 9.3 mmol) slowly at 0 °C. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water (10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed with brine (3 × 10 mL), dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexanes/ethyl aceteate = 30/1 to 10/1) to give methyl ether **7** (0.95 g, 58%, or 94% based on recovered starting material) as colorless oil and recovered alcohol **6S** (0.59 g): IR (neat, cm^{-1}) 2931, 2857, 1092, 835; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (dddd, J = 16.5, 10.1, 8.4, 6.1 Hz, 1H), 5.36 (td, J = 6.1, 1.2 Hz, 1H), 5.06−4.87 (m, 2H), 4.19 (d, J = 6.1 Hz, 2H), 3.42 (d, J = 2.6 Hz, 1H), 3.28 (s, 3H), 2.20−1.85 (m, 4H), 1.68−1.33 (m, 6H), 1.33−1.24 (m, 1H), 1.24−1.02 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.1, 126.1, 115.6, 75.7, 60.2, 56.2, 47.0, 43.5, 33.9, 31.7, 27.8, 27.7, 26.0, 19.9, 18.3, 12.6, −5.0; HRMS (ESI) calcd for $C_{20}H_{38}O_2SiLi^+$ $[M + Li]^+$ 345.2801, obsd 345.2808.

2-((1*S*,2*R*)-2-((*E*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-2-yl)-6-oxocyclohexyl)acetaldehyde (8). To a stirred solution of **6** (304 mg, 0.94 mmol) in dioxane (15 mL) and water (5 mL) were added 2,6-lutidine (0.23 mL, 2 mmol) at room temperature and then osmium tetraoxide solution (2.5% in *t*-BuOH, 0.25 mL, 0.002 mmol) and sodium periodate (0.84 g, 4 mmol). The reaction was stirred at room temperature for 3 h and extracted by ethyl acetate (3 × 30 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography to give **8** (150 mg, 50%) as colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.87−9.68 (m, 1H), 5.38 (dd, J = 6.0, 4.8 Hz, 1H), 4.18 (dd, J = 6.0, 0.6 Hz, 2H), 3.01 (ddd, J = 11.6, 8.8, 2.7 Hz, 1H), 2.80 (ddd, J = 17.8, 8.8, 1.1 Hz, 1H), 2.57−2.30 (m, 2H), 2.24 (dd, J = 17.8, 3.3 Hz, 1H), 2.12 (m, 2H), 1.91−1.75 (m, 2H), 1.75−1.62 (m, 1H), 1.59 (t, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.19, 200.83, 136.19, 128.14, 59.81, 53.94, 48.22, 41.36, 41.04, 30.59, 25.92, 18.34, 12.23, −5.10 (one carbon missing).

2-((1*S*,2*R*,6*R*)-2-((*E*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-2-yl)-6-methoxycyclohexyl)acetaldehyde (9). A solution of methyl ether **7** (2.8 g, 8.3 mmol) in acetone−H_2O (66 mL−25 mL) was treated with a solution of OsO_4 in *t*-BuOH (2.5%, 6.25 mL, 0.5 mmol) and NMO (1.45 g, 12.4 mmol) at 0 °C. The solution was brought to room temperature and stirred until **7** was consumed as indicated by TLC. The solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude was used in the next step without purification.

To a suspension of $NaIO_4$-impregnated silica gel[34] (16.6 g) in dichloromethane (40 mL) was added a solution of above reaction crude in dichloromethane (40 mL). The mixture was stirred at room temperature for 20 min before it was filtered. The filtrate was concentrated, and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to give aldehyde **9** (1.68 g, 4.9 mmol, 60%) as light yellow oil: IR (neat, cm^{-1}) 2934, 2889, 2824,1720; ^1H NMR (300 MHz, $CDCl_3$) δ 9.93−9.43 (m, 1H), 5.37 (td, J = 6.1, 1.0 Hz, 1H), 4.15 (dd, J = 6.1, 0.7 Hz, 2H), 3.37 (d, J = 2.7 Hz, 1H), 3.23 (s, 3H), 2.50 (ddd, J = 17.3, 7.8, 1.5 Hz, 1H), 2.39−2.11 (m, 2H), 2.11−1.89 (m, 2H), 1.56 (ddd, J = 10.8, 5.2, 2.7 Hz, 2H), 1.51−1.40 (m, 5H), 1.40−1.15 (m, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 138.4, 127.2, 77.7, 77.4, 77.0, 76.6, 60.0, 56.3, 46.1, 44.8, 38.8, 31.2, 27.5, 25.9, 19.5, 18.3, 12.6, −5.1; HRMS (ESI) calcd for $C_{19}H_{36}O_3SiLi^+$ $[M + Li]^+$ 347.2594, obsd 347.2610.

(*Z*)-1-((1*S*,2*R*,6*R*)-2-((*E*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-2-yl)-6-methoxycyclohexyl)-6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhex-3-en-2-one (11). To a solution of aldehyde **9** (200 mg, 0.59 mmol) and iodide **10** (317 mg, 0.71 mmol) in THF (15 mL) was added dropwise a solution of *t*-BuLi in heptane (1.7 M, 0.83 mL, 1.41 mmol) at −78 °C in 5 min. The reaction was maintained at this temperature for 30 min, quenched with satd aq NH_4Cl (5 mL), and extracted with EtOAc (3 × 30 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 15:1) to give a mixture of two diastereomeric allyl alcohols (208 mg) and recovered aldehyde **9** (33 mg).

The allyl alcohols (208 mg) were taken into anhydrous DMSO (10 mL) and treated with IBX (937 mg, 3.35 mmol). The solution was stirred at 30−35 °C for 3.5 h and extracted by diethyl ether (3 × 50 mL). The ether phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 15/1) to give ketone **11** (168 mg, 43% over two steps, or 52% based on recovered starting material) as colorless oil: IR (thin film, cm^{-1}) 2931, 2857, 1617, 1684, 1250, 1096; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75−7.57 (m, 4H), 7.48−7.29 (m, 6H), 6.06 (d, J = 1.2 Hz, 1H), 5.35 (dd, J = 6.2, 5.0 Hz, 1H), 4.28−4.02 (m, 2H), 3.82 (t, J = 6.4 Hz, 2H), 3.34 (s, 1H), 3.21 (s, 3H), 2.85 (dd, J = 12.8, 6.4 Hz, 2H), 2.51 (dd, J = 16.8, 8.8 Hz, 1H), 2.24 (dd, J = 16.8, 3.3 Hz, 1H), 2.05 (ddd, J = 17.8, 14.6, 7.5 Hz, 3H), 1.91 (d, J = 1.3 Hz, 3H), 1.56 (d, J = 13.2 Hz, 2H), 1.46 (d, J = 7.1 Hz, 4H), 1.38−1.14 (m, 2H), 1.03 (s, 9H), 0.89 (s, 10H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 156.3, 138.8, 135.6, 133.7, 129.5, 127.6, 126.7, 125.4, 63.3, 60.1, 56.5, 46.7, 44.3, 39.3, 36.9, 31.2, 27.6, 26.8, 26.3, 25.9, 19.7, 19.2, 18.3, 12.3, −5.0, −5.0; HRMS (ESI) calcd for $C_{40}H_{62}O_4Si_2Li^+$ $[M + Li]^+$ calcd 669.4347, obsd 669.4334.

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(*E*)-3-((1*R*,2*S*,3*R*)-2-((*Z*)-6-Hydroxy-4-methyl-2-oxohex-3-en-1-yl)-3-methoxycyclohexyl)but-2-enal (12). To a solution of ketone **11** (633 mg) in absolute ethanol (20 mL) was added PPTS (72 mg), and the mixture was stirred at 40 °C for 5 h. The solution was then concentrated *in vacuo*, and the residue was purified by column chromatography to give alcohol **11S** (419 mg, 80%) as colorless oil: IR (thin film, cm^{-1}) 3432, 2931, 2860, 1679, 1614, 1430, 1377, 1090; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.7, 1.7 Hz, 4H), 7.47−7.30 (m, 6H), 6.07 (s, 1H), 5.45 (t, J = 6.2 Hz, 1H), 4.08 (d, J = 6.8 Hz, 2H), 3.81 (t, J = 6.3 Hz, 2H), 3.34 (s, 1H), 3.30−3.12 (m, 3H), 2.94−2.73 (m, 2H), 2.50 (dd, J = 16.7, 8.1 Hz, 1H), 2.23 (dd, J = 16.7, 3.8 Hz, 1H), 2.19−1.96 (m, 3H), 1.91 (s, 3H), 1.64−1.41 (m, 5H), 1.29 (dd, J = 20.0, 18.1 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 156.8, 142.0, 135.6, 133.7, 129.7, 129.5, 127.7, 127.6, 125.3, 63.2, 59.2, 56.5, 46.9, 44.7, 39.3, 36.9, 31.3, 27.6, 26.8, 20.3, 19.6, 19.2, 12.4 (one carbon missing); HRMS (ESI) calcd for $C_{34}H_{49}O_4Si^+$ $[M + H]^+$ calcd 549.3400, obsd 549.3391.

To a solution of alcohol **11S** (101 mg, 0.184 mmol) in DMSO (1.84 mL) was added IBX (77 mg, 0.276 mmol). The solution was stirred at room temperature for 2 h and extracted by diethyl ether (3 × 30 mL). The ether phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to give aldehyde **12** (85 mg, 85%) and its geometric isomer (not shown) due to isomerization of the enal alkene (4.7:1). For **12**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.92 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 5.4 Hz, 4H), 7.34 (d, J = 6.2 Hz, 6H), 6.03 (s, 1H), 5.87 (d, J = 7.8 Hz, 1H), 3.80 (t, J = 5.9 Hz, 2H), 3.35 (s, 1H), 3.18 (s, 3H), 2.83 (dt, J = 12.1, 5.9 Hz, 2H), 2.72−2.46 (m, 1H), 2.44−2.27 (m, 1H), 2.27−1.97 (m, 7H), 1.88 (s, 3H), 1.70−1.43 (m, 3H), 1.43−1.17 (m, 2H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 191.2, 166.5, 157.5, 135.7, 133.8, 129.7, 128.7, 127.8, 125.3, 76.8, 63.3, 61.8, 56.6, 48.1, 44.4, 39.2, 37.1, 31.2, 27.5, 27.0, 19.5; HRMS (ESI) calcd for $C_{34}H_{47}O_4Si^+$ $[M + H]^+$ 547.3244, obsd 547.3210.

To a mixture of aldehyde **12** (29 mg, 0.053 mmol) and ethyl diazoacetate (26 μL, 0.21 mmol) in anhydrous dichloromethane (1.5 mL) was added tin(II) chloride (13 mg, 0.067 mmol). The mixture was maintained at 30−35 °C for 24 h before it was concentrated. The residue was purified by column chromatography to give β-keto ester **17** that existed as a mixture of its keto and enol forms (~10:1, 22 mg, 0.035 mmol, 66%).

(*Z*)-6-((1*S*,2*R*,6*R*)-2-Methoxy-6-((*E*)-4-oxobut-2-en-2-yl)cyclohexyl)-3-methyl-5-oxohex-3-en-1-yl 2-Bromoacetate (13). To a solution of aldehyde **12** (17 mg, 0.21 mmol) in THF (3.9 mL) were added a solution of TBAF in THF (1 M, 235 mL, 0.235 mmol) and HOAc (13.5 mL, 0.235 mmol) at 0 °C. The mixture was allowed to room temperature in 3 h and stirred overnight. The reaction was quenched with satd aq NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give alcohol **12S1** (22 mg, 33%) and the isomeric alcohol **12S2** (19 mg, 28%). Part of **12** (5.4 mg) was also recovered.

To a solution of alcohol **12S1** (63 mg, 0.20 mmol) in dichloromethane (2 mL) were added pyridine (19.7 mL, 0.244 mmol) and bromoacetyl bromide (21.3 mL, 0.244 mol) at −78 °C. The reaction was stirred at the same temperature for 1 h before it was quenched with water (2 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to give **13** as a light yellow oil (50 mg, 57%): IR (neat, cm^{-1}) 2932, 2859, 1739, 1669, 1446; ^1H NMR (300 MHz, $CDCl_3$) δ 9.93 (d, J = 8.0 Hz, 1H), 6.09 (s, 1H), 5.86 (d, J = 8.0 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 3.80 (s, 2H), 3.38 (s, 1H), 3.23 (s, 3H), 2.86 (td, J = 6.6, 2.4 Hz, 2H), 2.59 (dd, J = 18.1, 9.5 Hz, 1H), 2.42−2.24 (m, 1H), 2.24−2.10 (m, 2H), 2.04 (s, 3H), 1.91 (s, 3H), 1.57 (m, 3H), 1.46−1.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 191.2, 167.0, 166.4, 154.1, 128.5, 126.1, 76.7, 64.7, 56.4, 47.8, 44.3, 38.8, 32.8, 30.9, 29.6, 27.2, 26.3, 25.8, 19.2; HRMS (ESI) calcd for $C_{20}H_{30}BrO_5^+$ $[M + H]^+$ 429.1277, obsd 429.1267.

(1*E*,9*Z*,12a*S*,13*R*,16a*R*)-13-Methoxy-1,9-dimethyl-7,8,12a,13,14,15,16,16a-octahydro-3*H*-benzo[*g*][1]-oxacyclotetradecine-3,5,11(4*H*,12*H*)-trione (15). To a mixture of Li wires (56 mg, 7.9 mmol), naphthalene (1.04 g, 7.9 mmol), and pieces of broken glass chips was added anhydrous THF (4 mL) under N_2. The mixture was vigorously stirred while its color changed to dark green within 30 s. After being stirred at room temperature for 2 h, the mixture was cooled to 0 °C, and a solution of flame-dried $ZnCl_2$ (0.669 g, 4.8 mmol) in THF (5 mL) was introduced via a cannula. This mixture was stirred for 45 min to form a black Reike zinc suspension.

To the Rieke Zn suspension (3.22 mL) was added dropwise a solution of bromide **14** (18 mg, 0.043 mmol) in THF (4 mL) at 0 °C in 90 min. The mixture was stirred for another 15 min before the reaction was quenched with satd aq NH_4Cl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/1) to give alcohol **13S** (13 mg, 84%) as colorless oil.

To a solution of alcohol **13S** (7.3 mg, 0.021 mmol) in DMSO (0.2 mL) was added IBX (8.8 mg, 0.03 mmol), and the mixture was stirred at room temperature for 4 h. Direct column chromatography purification of the reaction crude gave lactone **15** (6.7 mg, 92%) as colorless oil: IR (neat, cm^{-1}) 2931, 2854, 1738, 1681, 1607; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.95 (s, 1H), 4.26 (m, 2H), 3.44 (d, J = 13.6 Hz, 1H), 3.35 (s, 1H), 3.27 (d, J = 13.8 Hz, 4H), 2.53−2.31 (m, 2H), 2.23−2.05 (m, 4H), 2.05−1.91 (m, 1H), 1.88 (t, J = 7.5 Hz, 3H), 1.73 (d, J = 13.1 Hz, 1H), 1.61−1.45 (m, 3H), 1.43−1.11 (m, 3H), 0.87 (t, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 192.0, 167.0, 165.1, 152.3, 126.8, 123.4, 80.4, 62.2, 56.5, 50.6, 49.4, 48.3, 37.9, 32.1, 31.3, 29.7, 27.3, 24.1, 19.6; HRMS (ESI) calcd for $C_{20}H_{29}O_5^+$ $[M + H]^+$ 349.2015, obsd 349.2027.

(4a*S*,4b*S*,6a*S*,7*R*,10a*R*,10b*R*)-12-Hydroxy-7-methoxy-4a,10b-dimethyl-4,4a,4b,6,6a,7,8,9,10,10a,10b,11-dodecahydro-1*H*-naphtho[2,1-*f*]isochromene-1,5(3*H*)-dione (16). To a solution of TBAF (1 M in THF, 37 μL, 0.037 mmol) in THF (0.7 mL) was added lactone **15** (6.7 mg, 0.019 mmol) in THF (0.78 mL) at −78 °C over 1 min via a cannula, which was further rinsed with DMF (1.27 mL). The reaction flask was transferred to an ice−water bath and stirred for 2 h. The reaction was quenched with satd aq NH_4Cl (0.5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 1/1) to give compound **16** (5.9 mg, 88%) as a white solid: IR (thin film, cm^{-1}) 2934, 1702, 1640, 1610, 1415, 1211, 1092; ^1H NMR (500 MHz, $CDCl_3$) δ 13.23 (s, 1H), 4.47 (dd, J = 17.2, 7.1 Hz, 1H), 4.34 (dd, J = 11.7, 3.4 Hz, 1H), 3.29 (s, 3H), 3.17 (s, 1H), 2.48 (d, J = 17.5 Hz, 2H), 2.43 (dd, J = 13.1, 7.1 Hz, 1H), 2.25−2.14 (m, 2H), 2.14−1.98 (m, 2H), 1.80 (d, J = 9.5 Hz, 2H), 1.56 (d, J = 10.4 Hz, 2H), 1.48 (d, J = 14.2 Hz, 1H), 1.40 (s, 1H), 1.36 (s, 3H), 1.31 (s, 3H), 1.19 (M, 2H), 1.09−0.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 175.1, 171.2, 98.5, 79.3, 66.2, 65.2, 56.8, 44.0, 43.3, 42.5, 42.1, 34.2, 34.0, 33.3, 31.3, 27.4, 26.8, 25.4, 19.7; HRMS (ESI) calcd for $C_{20}H_{28}O_5Li^+$ $[M + Li]^+$ calcd 355.2097, obsd 355.2113.

(*E*)-1-((1*S*,2*R*,6*R*)-2-((*E*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-2-yl)-6-methoxycyclohexyl)-6-((*tert*-butyldiphenylsilyl)-oxy)-4-methylhex-3-en-2-one (20). To a solution of aldehyde **9** (646 mg, 1.9 mmol) and vinyl iodide **19** (1.03 g, 2.28 mmol) in THF (14 mL) was added dropwise a solution of *t*-BuLi in heptane (1.7 M, 0.79 mL, 1.34 mmol) at −78 °C. The reaction was stirred at the same temperature for 20 min before it was quenched with satd aq NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to give **20S** as a diastereomeric mixture of allylic alcohols (670 mg, 1.01 mmol, 53%).

To a solution of **20S** (752 mg, 1.13 mmol) in DMSO (11 mL) was added IBX (475 mg, 1.7 mmol). The solution was stirred at room temperature for 3.5 h before it was extracted with diethyl ether (3 × 50 mL). The combined ether extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column

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chromatography (hexanes/ethyl acetate = 10/1) to give ketone **20** (648 mg, 1.00 mmol, 86%) as colorless oil: IR (thin film, cm^{-1}) 2928, 2857, 1688, 1620, 1463, 1359, 1093; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76−7.55 (m, 4H), 7.50−7.30 (m, 6H), 6.03 (s, 1H), 5.35 (t, J = 6.1 Hz, 1H), 4.25−4.03 (m, 2H), 3.78 (t, J = 6.5 Hz, 2H), 3.38 (s, 1H), 3.22 (s, 3H), 2.56 (dd, J = 17.0, 9.1 Hz, 1H), 2.33 (t, J = 6.4 Hz, 2H), 2.24 (dd, J = 17.0, 2.7 Hz, 1H), 2.19−1.91 (m, 5H), 1.70−1.52 (m, 3H), 1.45 (s, 3H), 1.37−1.12 (m, 3H), 1.04 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 154.3, 138.8, 135.4, 133.5, 129.6, 127.6, 126.6, 125.6, 76.9, 61.8, 60.0, 56.4, 46.5, 44.2, 44.0, 39.1, 31.2, 27.5, 26.7, 25.9, 19.6, 19.3, 19.1, 18.2, 12.3, −5.1; HRMS (ESI) calcd for $C_{40}H_{62}O_4Si_2Li^+$ $[M + Li]^+$ 669.4347, obsd 669.4343.

(*E*)-3-((1*R*,2*S*,3*R*)-2-((*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-2-oxohex-3-en-1-yl)-3-methoxycyclohexyl)but-2-enal (21). To a solution of **20** (621 mg, 0.937 mmol) in ethanol (15 mL) was added PPTS (70 mg, 0.28 mmol). The solution was maintained at 30 °C for 2 h before it was concentrated. The residue was filtered through a pad of silica gel (hexanes/ethyl acetate = 10/1 to 1/1). The filtrate was concentrated and the residue was taken into DMSO (15 mL). The solution was treated with IBX (444 mg, 1.59 mmol) and stirred at room temperature for 2 h before it was extracted with diethyl ether (3 × 50 mL). The combined ether phase was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography to give aldehyde **21** (440 mg, 86% over two steps) as colorless oil: IR (thin film, cm^{-1}) 2931, 2857, 1670, 1620, 1427, 11359, 1196, 1090; ^1H NMR (300 MHz, $CDCl_3$) δ 9.96 (d, J = 8.0 Hz, 1H), 7.80−7.54 (m, 4H), 7.39 (m, 6H), 6.02 (d, J = 1.2 Hz, 1H), 5.89 (dd, J = 8.0, 1.1 Hz, 1H), 3.79 (t, J = 6.4 Hz, 2H), 3.41 (d, J = 3.0 Hz, 1H), 3.22 (s, 3H), 2.63 (dd, J = 16.9, 8.9 Hz, 1H), 2.45−2.27 (m, 3H), 2.27−2.12 (m, 2H), 2.12−1.95 (m, 7H), 1.74−1.48 (m, 3H), 1.34 (m, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 191.2, 166.5, 155.5, 135.5, 133.5, 129.7, 128.5, 127.7, 125.3, 76.6, 61.7, 56.5, 47.8, 44.1, 44.0, 38.8, 31.1, 27.3, 26.8, 19.5, 19.3, 19.2, 14.2 (one carbon missing); HRMS (ESI) calcd for $C_{34}H_{47}O_4Si^+$ $[M + H]^+$ 547.3244, obsd 547.3265.

(*E*)-Ethyl 5-((1*R*,2*S*,3*R*)-2-((*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-2-oxohex-3-en-1-yl)-3-methoxycyclohexyl)-3-oxohex-4-enoate (21S). To a solution of aldehyde **21** (58 mg, 0.105 mmol) and ethyl diazoacetate (51.3 μL, 0.42 mmol) in dichloromethane (3 mL) was added tin(II) chloride (25 mg, 0.133 mmol). The mixture was stirred at 30−35 °C overnight before it was concentrated. The residue was purified by column chromatography to give β-keto ester **21S** (36 mg, 0.057 mmol, 54%) a mixture (~10:1) of its keto and enol forms: ^1H NMR (300 MHz, $CDCl_3$) δ 12.22 (s, 0.1H), 7.72−7.58 (m, 4H), 7.49−7.31 (m, 6H), 6.12 (s, 1H), 6.04 (s, 1H), 6.01 (s, 1H), 5.61 (s, 0.1H), 4.91 (s, 0.1H), 4.17 (dt, J = 8.3, 6.6 Hz, 2H), 3.77 (td, J = 6.4, 2.6 Hz, 2H), 3.42 (s, 3H), 3.21 (s, 3H), 2.60 (dd, J = 16.7, 9.0 Hz, 1H), 2.32 (dd, J = 12.5, 6.2 Hz, 2H), 2.28−2.11 (m, 3H), 2.05 (m, 6H), 1.99 (m, 2H), 1.93−1.88 (m, 1H), 1.79−1.71 (m, 1H), 1.67−1.46 (m, 1 H), 1.38 (m, 1H), 1.33−1.19 (m, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, cdcl$_3$) δ 200.32, 192.11, 167.62, 164.58, 155.46, 135.52, 133.52, 129.70, 127.68, 125.29, 123.14, 61.79, 61.14 (two carbons missing due to signal overlapping); HRMS (ESI) calcd for $C_{38}H_{52}O_6SiLi^+$ $[M + Li]^+$ 639.3693, found 639.3703.

(*E*)-Ethyl 5-((1*R*,2*S*,3*R*)-2-((*E*)-6-Hydroxy-4-methyl-2-oxohex-3-en-1-yl)-3-methoxycyclohexyl)-3-oxohex-4-enoate (22). To a solution of β-keto ester **21S** (192 mg, 0.304 mmol) in THF (17 mL) were added a solution of TBAF in THF (1 M, 1.22 mL, 1.22 mmol) and acetic acid (70 μL, 1.22 mmol) at 0 °C. The solution was allowed to warm room temperature over 2 h and stirred until the reaction was complete as indicated by TLC. The solution was concentrated *in vacuo*, and the residue was purified by column chromatography to give alcohol **22** as colorless oil (59 mg, 50%): IR (thin film, cm^{-1}) 3470, 2937, 1714, 1682, 1608; ^1H NMR (300 MHz, $CDCl_3$) δ 12.21 (s, 0.23H, enol form), 6.10 (d, J = 0.9 Hz, 1H), 6.06 (d, J = 1.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.78 (t, J = 6.2 Hz, 2H), 3.43 (s, 3H), 3.41 (s, 1H), 3.25 (s, 3H), 2.57 (dd, J = 17.7, 8.8 Hz, 1H), 2.36 (t, J = 6.2 Hz, 2H), 2.22 (m, 2H), 2.17−2.10 (m, 3H), 2.09−1.94 (m, 4H), 1.77 (m, 2H), 1.66−1.44 (m, 3H), 1.38 (m,1H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 192.2, 167.8, 164.6, 154.6, 125.5, 123.2, 77.0, 61.2, 60.1, 56.4, 50.8, 48.4, 44.6, 44.3, 44.0, 39.1, 31.3, 27.3, 19.3, 19.2, 14.1; HRMS (ESI) calcd for $C_{22}H_{34}O_6Na^+$ $[M + Na]^+$ 417.2253, obsd 417.2242.

(1*E*,3*Z*,9*E*,12a*S*,13*R*,16a*R*)-3-Hydroxy-13-methoxy-1,9-dimethyl-7,8,12a,13,14,15,16,16a-octahydro-5*H*-benzo[*g*][1]oxacyclotetradecine-5,11(12*H*)-dione (24). A solution of alcohol **22** (50 mg, 0.127 mmol) in anhydrous toluene (69 mL) was refluxed under a N_2 atmosphere for 20 h before it was concentrated *in vacuo*. Purification by column chromatography (silica gel, hexane/EtOAc = 2/1) gave lactone **24** as colorless oil (33 mg, 76%): IR (thin film, cm^{-1}) 2934, 1741, 1682, 1620,1368, 1276, 1090; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (s, 1H), 5.93 (d, J = 1.2 Hz, 1H), 4.55 (ddd, J = 11.3, 6.9, 4.2 Hz, 1H), 4.09 (ddd, J = 11.7, 7.8, 4.2 Hz, 1H), 3.46 (d, J = 12.3 Hz, 1H), 3.39 (s, 1H), 3.30 (s, 3H), 3.24 (d, J = 12.3 Hz, 1H), 2.68 (dd, J = 15.8, 8.5 Hz, 1H), 2.52 (ddd, J = 11.0, 7.3, 4.7 Hz, 1H), 2.46−2.33 (m, 1H), 2.33−2.17 (m, 2H), 2.17−1.99 (m, 5H), 1.92 (d, J = 0.9 Hz, 3H), 1.58−1.44 (m, 3H), 1.33 (ddd, J = 16.9, 13.0, 5.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 190.4, 166.7, 166.7, 152.8, 126.1, 123.6, 80.5, 61.1, 56.5, 51.8, 50.4, 48.0, 40.2, 39.1, 30.2, 27.5, 19.1, 19.0, 16.8.; HRMS (ESI) calcd for $C_{20}H_{29}O_5^+$ $[M + H]^+$ 349.2015, obsd 349.2012.

(4a*R*,4b*S*,6a*S*,7*R*,10a*R*,10b*S*)-12-Hydroxy-7-methoxy-4a,10b-dimethyl-4,4a,4b,6,6a,7,8,9,10,10a,10b,11-dodecahydro-1*H*-naphtho[2,1-*f*]isochromene-1,5(3*H*)-dione (25). To a solution of TBAF (1 M in THF, 33 μL, 0.033 mmol) in THF (0.5 mL) was added lactone **24** (6.7 mg, 0.017 mmol) in THF (0.83 mL) at −78 °C over 1 min via a cannula, which was further rinsed with DMF (1.14 mL). The reaction was allowed to 0 °C and stirred for 3 h before it was quenched with satd aq NH_4Cl (0.5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate =2/1) to give polycyclic compound **25** (5.4 mg, 93%): IR (thin film, cm^{-1}) 2940, 1706, 1643, 1211, 1093; ^1H NMR (300 MHz, $CDCl_3$) δ 13.03 (s, 1H), 4.69−4.50 (m, 1H), 4.47−4.31 (m, 1H), 3.31 (s, 3H), 3.18 (s, 1H), 2.84−2.62 (m, 1H), 2.37 (d, J = 2.9 Hz, 2H), 2.26 (ddd, J = 19.0, 11.9, 4.1 Hz, 2H), 2.09 (d, J = 12.3 Hz, 1H), 1.75 (d, J = 12.6 Hz, 2H), 1.68−1.56 (m, 2H), 1.53−1.36 (m, 4H), 1.20 (dd, J = 20.7, 9.4 Hz, 3H), 1.04 (s, 3H), 0.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 171.0, 170.1, 102.3, 78.0, 66.2, 62.9, 56.7, 47.4, 45.5, 42.8, 41.8, 40.3, 35.9, 33.3, 27.7, 24.8, 21.9, 19.5, 18.8, 13.4; HRMS (ESI) calcd for $C_{20}H_{29}O_5^+$ $[M + H]^+$ 349.2015, obsd 349.2022.

(1*Z*,9*E*,12a*S*,16a*R*)-9-(2-((4-Methoxybenzyl)oxy)ethyl)-1,15-dimethyl-7,8,12,12a,16,16a-hexahydro-3*H*-benzo[*g*][1]oxacyclotetradecine-3,5,11,13(4*H*)-tetraone (28). A solution of alcohol **26**[8] (0.62 g, 1.1 mmol) in toluene (350 mL) was refluxed under an N_2 atmosphere for 19 h before it was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 1/1 to 1/2) to give lactones **27** (0.27 g, 46%) and **28** (57 mg, 6%) as colorless oil. Compound **28**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.18 (m, 2H), 6.90−6.81 (m, 2H), 6.07 (s, 1H), 5.96 (s, 1H), 5.95 (dd, J = 2.3, 1.3 Hz, 1H), 4.62 (td, J = 11.4, 3.7 Hz, 1H), 4.58−4.44 (m, 1H), 4.41 (s, 2H), 4.08 (ddd, J = 11.2, 4.7, 3.1 Hz, 1H), 3.79 (s, 3H), 3.69 (dt, J = 9.1, 5.7 Hz, 1H), 3.62−3.50 (m, 1H), 3.46 (d, J = 13.0 Hz, 1H), 3.30−3.15 (m, 2H), 3.15−2.96 (m, 2H), 2.75−2.58 (m, 1H), 2.58−2.48 (m, 2H), 2.48−2.32 (m, 2H), 2.02 (dd, J = 17.7, 4.4 Hz, 1H), 1.95 (s, 3H), 1.82 (dd, J = 5.9, 1.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 198.0, 190.3, 166.6, 162.0, 160.4, 159.1, 153.9, 130.3, 129.2, 128.7, 125.8, 124.8, 113.7, 72.6, 69.5, 61.0, 55.3, 52.8, 45.5, 42.1, 41.4, 38.9, 34.1, 31.2, 24.3, 21.6; HRMS (ESI) calcd for $C_{29}H_{34}O_7Li^+$ $[M + Li]^+$ 501.2465, obsd 501.2441.

(*Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-3-methylhept-2-en-1-ol (30S1). A solution of DIBAL-H in toluene (1 M, 50.6 mL, 50.6 mmol) was added to a stirred solution of **30** (6.2 g, 20.6 mmol) in CH_2Cl_2 (30 mL) at −78 °C dropwise and stirred at the same temperature for 30 min. The reaction was quenched with MeOH (10 mL) followed by satd aq potassium sodium tartrate (30 mL) at 0 °C. The mixture was allowed to room temperature and filtered through a pad of Celite with ethyl acetate (100 mL) as the eluent. The combined filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column

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chromatography (hexanes/ethyl acetate = 3/1) to give alcohol **30S1** (4.9 g, 92% for two steps) as colorless oil: IR (thin film, cm^{-1}): 3344, 2931, 1472, 1255, 1101, 837; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (t, J = 7.1 Hz, 1H), 4.11 (d, J = 7.1 Hz, 2H), 3.60 (t, J = 6.1 Hz, 2H), 2.08 (t, J = 7.2 Hz, 2H), 1.73 (s, 3H), 1.54−1.36 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 124.2, 62.9, 59.0, 32.5, 31.5, 25.9, 24.4, 23.4, 18.3, −5.3; HRMS (ESI) calcd for $C_{14}H_{31}O_2Si^+$ $[M + H]^+$ 259.2093, obsd 259.2090.

(*Z*)-7-((4-Methoxybenzyl)oxy)-5-methylhept-5-en-1-ol (30S3). A solution of alcohol **30S1** (10.2 g, 39.5 mmol) in THF (30 mL) was added to a suspension of NaH (2.37 g, 59.3 mmol, 60%) in THF (20 mL) dropwise at 0 °C. The mixture was stirred for 30 min before a solution of PMBBr (9.48 g, 47.4 mmol) in THF (15 mL) was added dropwise. The reaction was stirred for 3 h at room temperature before it was quenched with water (30 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude (*Z*)-*tert*-butyl((7-((4-methoxybenzyl)oxy)-5-methylhept-5-en-1-yl)oxy)-dimethylsilane **30S2** (15 g) as clear oil.

A solution of TBAF in THF (1 M, 59.5 mL, 59.5 mmol) was added to a solution of above crude **30S2** in THF (50 mL) and stirred for at room temperature for 1 h. The mixture was quenched with aq NH_4Cl (30 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 3/2) to give alcohol **30S3** (8.0 g, 65% over two steps): IR (thin film, cm^{-1}) 3406, 2936, 2861, 1613, 1514, 1249, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.41 (t, J = 7.0 Hz, 1H), 4.42 (s, 2H), 3.96 (d, J = 7.0 Hz, 2H), 3.79 (s, 3H), 3.59 (t, J = 6.3 Hz, 2H), 2.05 (t, J = 7.3 Hz, 2H), 1.73 (dd, J = 2.3, 1.0 Hz, 3H), 1.59−1.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 140.7, 130.5, 129.4, 121.8, 113.7, 71.7, 65.8, 62.6, 55.2, 32.3, 31.7, 24.2, 23.3.

(*Z*)-7-((4-Methoxybenzyl)oxy)-5-methylhept-5-enal (31). To a stirred solution of alcohol **30S3** (8.0 g, 30.3 mmol) in CH_2Cl_2 (20 mL) were added IBX (12.7 g, 45.4 mmol) and DMSO (5 mL) at 0 °C. The mixture was stirred at room temperature for 4 h before it was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 9/1) to give aldehyde **31** (6.7 g, 85%): IR (thin film, cm^{-1}) 2940, 2839, 1723, 1698, 1602, 1513, 1259, 1161; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, J = 1.6 Hz, 1H), 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.46 (t, J = 6.9 Hz, 1H), 4.42 (s, 2H), 3.94 (d, J = 7.0 Hz, 2H), 3.80 (s, 3H), 2.38 (t, J = 7.3 Hz, 2H), 2.08 (t, J = 7.6 Hz, 2H), 1.74 (s, 3H), 1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 159.0, 39.4, 130.3, 129.3, 122.6, 113.6, 71.7, 65.7, 55.1, 43.0, 30.9, 23.0, 20.1; HRMS (ESI) calcd for $C_{16}H_{22}O_3^+$ $[M + Li]^+$ 269.1729, obsd 269.1740.

(1*S*,2*R*)-2-((*E*)-1-Iodoprop-1-en-2-yl)cyclohexanol (32S). To a stirred suspension of zirconocene dichloride (1.66 g, 5.67 mmol) in anhydrous CH_2Cl_2 (100 mL) was added a solution of trimethylaluminum (2 M in hexane, 40.0 mL, 80.0 mmol) dropwise via cannula at −20 °C. The resulting yellow mixture was stirred for 10 min before water (0.71 mL, 39.99 mmol) was added dropwise. After an additional 10 min, a solution of 2-ethynylcyclohexanol **32** (3.2 g, 25.8 mmol) in CH_2Cl_2 (20 mL), pretreated with Me_3Al (4.0 mL, 7.99 mmol), was added dropwise via cannula at 0 °C. The mixture was allowed to room temperature, and the resulting yellow thick slurry was stirred for 5 h. The reaction mixture was then cooled to −20 °C, and a solution of I_2 (8.0 g, 31 mmol) in ether (50 mL) was added dropwise via cannula. The mixture was allowed to room temperature and was stirred for additional 5 h. The reaction mixture was slowly poured into a well-stirred mixture of a satd aq sodium potassium tartrate (200 mL) and ether (200 mL), and the biphasic mixture stirred for 2 h before the slurry was filtered through Celite. The layers of the mixture were separated and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were washed with aq $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 1/4) to give alcohol **32S** (3.5 g, 51%): IR (thin film, cm^{-1}) 3386, 2930, 2856, 1448, 1270, 1062; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 3.45 (td, J = 10.0, 4.3 Hz, 1H), 2.15 (ddd, J = 8.3, 7.1, 3.1 Hz, 1H), 2.08−1.99 (m, 1H), 1.81 (s, 3H) 1.78−1.58 (m, 5H), 1.42−1.14 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 77.3, 70.8, 67.6, 56.7, 34.5, 30.2, 25.5, 24.7, 20.7; HRMS (ESI) calcd for $C_9H_{16}IO^+$ $[M + H]^+$ 267.0246, obsd 267.0251.

***tert*-Butyl(((1*S*,2*R*)-2-((*E*)-1-iodoprop-1-en-2-yl)cyclohexyl)-oxy)dimethylsilane (33).** To a stirred solution of alcohol **32S** (3.5 g, 13.1 mmol) in anhydrous CH_2Cl_2 (20 mL) was sequentially treated with imidazole (1.34 g, 19.7 mmol) and TBSCl (2.57 g, 17.1 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min before it was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluted with hexanes, to give silyl ether **33** (4.5 g, 90%): IR (thin film, cm^{-1}) 2928, 2857, 1463, 1362, 1253, 1096; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (s, 1H), 3.43 (td, J = 9.8, 4.7 Hz, 1H), 2.20 (ddd, J = 9.7, 8.5, 3.3 Hz, 1H), 1.76 (s, 3H), 1.74−1.56 (m, 4H), 1.26 (m, 4H), 0.84 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 76.8, 72.6, 56.2, 36.4, 30.5, 25.8, 25.5, 25.0, 21.6, 17.9, −4.0, −4.8; HRMS molecular ion not observed.

(2*E*,8*Z*)-2-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-cyclohexyl)-10-((4-methoxybenzyl)oxy)-8-methyldeca-2,8-dien-4-ol (34). To a stirred solution of vinyl iodide **33** (4.4 g, 11.5 mmol) in anhydrous THF (30 mL) was added Me_2Zn (9.64 mL, 11.5 mmol) and a solution of *t*-BuLi in hexanes (1.7 M, 13.6 mL, 23.1 mmol) at −78 °C. After 10 min, a solution of aldehyde **31** (2.52 g, 9.6 mmol) in anhydrous THF (20 mL) was added dropwise at −78 °C. The reaction mixture was stirred for 30 min before it was quenched with satd aq NH_4Cl (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and purified by silica gel column chromatography (hexanes/ethyl acetate = 9/1) to give alcohol **34** (3.4 g, 70%) as viscous oil: IR (thin film, cm^{-1}): 3420, 2930, 2856, 1717, 1612, 1514, 1249, 1094, 1037, 836; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.39 (t, J = 6.2 Hz, 1H), 5.22 (dd, J = 8.5, 1.3 Hz, 1H), 4.42 (s, 2H), 3.97 (d, J = 6.9 Hz, 2H), 3.80 (s, 3H), 3.48 (td, J = 9.6, 4.3 Hz, 1H), 2.11−1.83 (m, 2H), 1.73 (s, 3H), 1.66 (s, 3H), 1.62 (s, 1H), 1.59−1.13 (m, 14H), 0.83 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 146.5, 145.4, 135.4, 134.2, 133.2, 126.7, 118.5, 78.2, 76.5, 73.0, 70.8, 60.2, 60.0, 42.0, 41.2, 36.7, 36.0, 30.6, 30.5, 29.9, 28.7, 28.2, 22.8, 19.8, 1.1, 0.0; HRMS (ESI) calcd for $C_{31}H_{53}O_4Si^+$ $[M + H]^+$ 517.3713, obsd 517.3716.

(2*Z*,8*E*)-9-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-cyclohexyl)-3-methyldeca-2,8-diene-1,7-diol (34S). To a stirred solution of PMB ether **34** (3.2 g, 6.2 mmol) in CH_2Cl_2 (15 mL) were added DDQ (1.69 g, 7.4 mmol) and water (1.5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min before it was quenched with satd aq $NaHCO_3$ (20 mL). The mixture was diluted with CH_2Cl_2 (30 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 3/1) to give diol **34S** (1.71 g, 70%) as viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (t, J = 7.1 Hz, 1H), 5.22 (d, J = 8.5 Hz, 1H), 4.35 (dt, J = 8.4, 6.0 Hz, 1H), 4.10 (d, J = 7.1 Hz, 2H), 3.48 (ddd, J = 14.1, 4.9 Hz, 1H), 2.19−1.98 (m, 2H), 1.96−1.82 (m, 3H), 1.72 (s, 3H), 1.65 (s, 3H), 1.62−1.10 (m, 11H), 0.82 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 140.0, 128.5, 124.3, 73.2, 68.2, 58.9, 55.5, 37.0, 36.4, 31.6, 31.2, 25.8, 25.6, 25.0, 23.9, 23.4, 18.0, 14.7, −3.7, −4.8; HRMS (ESI) calcd for $C_{23}H_{45}O_3Si^+$ $[M + H]^+$ 397.3138, obsd 397.3156.

(2*Z*,8*E*)-9-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-cyclohexyl)-3-methyl-7-oxodeca-2,8-dienal (35). To a stirred solution of the diol **34S** (1.6 g, 4.0 mmol) in anhydrous CH_2Cl_2 (10 mL) were added IBX (3.39 g, 12.12 mmol) and DMSO (2 mL) at 0 °C. The mixture was stirred at room temperature for 8 h before it was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 9/1) to give dicarbonyl compound **35** and its isomer due to enal alkene isomerization (~ 4:1, 1.1 g, 70%). For **35**: IR (thin film, cm^{-1}) 2931, 2857, 1687, 1614, 1448, 1250, 1098, 836; ^1H NMR (300 MHz,

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$CDCl_3$) δ 9.93 (d, J = 8.2 Hz, 1H), 6.07 (s, 1H), 5.87 (d, J = 8.2 Hz, 1H), 3.52 (td, J = 9.7, 4.5 Hz, 1H), 2.62−2.51 (m, 1H), 2.44 (t, J = 7.1 Hz, 2H), 2.09 (s, 3H), 1.96 (s, 3H), 2.05−1.88 (m, 2H), 1.88−1.55 (m, 6H), 1.41−1.09 (m, 4H), 0.79 (s, 9H), −0.01 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 190.7, 163.9, 161.6, 128.7, 124.2, 72.8, 57.4, 43.1, 36.1, 31.8, 30.1, 25.7, 25.2, 24.9, 24.8, 22.8, 17.9, 17.2, −3.9, −5.1; HRMS (ESI) calcd for $C_{23}H_{41}O_3Si^+$ $[M + H]^+$ 393.2825, obsd 393.2832.

(4*Z*,10*E*)-Ethyl 11-((1*R*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)-cyclohexyl)-5-methyl-3,9-dioxododeca-4,10-dienoate (36). To a stirred solution of aldehyde **35** (0.50 g, 1.27 mmol) and ethyl diazoacetate (0.26 mL, 2.55 mmol) in dichloromethane (7.5 mL) was added $SnCl_2$ (48 mg, 0.255 mmol) at room temperature. This mixture was stirred for 6 h at room temperature before it was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to give β-ketoester **36** as a mixture of two inseparable isomers (0.42 g, 70%), each of which also existed in enol and keto forms: IR (thin film, cm^{-1}) 2931, 2857, 1738, 1688, 1613, 1250, 1097, 836; HRMS (ESI) calcd for $C_{27}H_{47}O_5Si^+$ $[M + H]^+$ 479.3193, obsd 479.3175.

(4*Z*,10*E*)-Ethyl 11-((1*R*,2*S*)-2-hydroxycyclohexyl)-5-methyl-3,9-dioxododeca-4,10- dienoate (36S). To a stirred solution of β-keto ester **36** (200 mg, 0.418 mmol) in MeOH (14 mL) was added 5% HCl (0.2 mL). The reaction was stirred at room temperature for 20 min before it was quenched with satd aq $NaHCO_3$ (10 mL). The mixture was stirred at room temperature for an additional 5 min and extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with satd aq $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. After concentration *in vacuo*, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7/3) to provide alcohol **36S** as a mixture of inseparable isomers (114 mg, 75%), each of which existed in keto and enol forms, as colorless oil: IR (thin film, cm^{-1}) 3455, 2932, 2858, 1738, 1684, 1614, 1448, 1246, 1032, 857; HRMS (ESI) calcd for $C_{21}H_{33}O_5^+$ $[M + H]^+$ 365.2328, obsd 365.2310.

(5*Z*,11*E*,12a*R*,16a*S*)-6,12-Dimethyl-8,9,12a,13,14,15,16,16a-octahydro-2*H*-benzo[*b*][1]oxacyclotetradecine-2,4,10(3*H*,7*H*)-trione (37). A solution of alcohol **36S** (90 mg, 0.247 mmol) in toluene (2 mL) was refluxed under N_2 for 36 h before it was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 19/1) to give *Z*,*E*-lactone **37** as colorless oil (13.0 mg, 17%) and *E*,*E*- lactone (5*E*,11*E*,12a*R*,16a*S*)-6,12-dimethyl-8,9,12a,13,14,15,16,16a-octahydro-2*H*-benzo[*b*][1]-oxacyclotetradecine-2,4,10(3*H*,7*H*)-trione **37S** (20.0 mg, 25%). Compound **37**: IR (thin film, cm^{-1}): 2932, 2860, 1734, 1687, 1616, 1448, 1259, 1164, 1105, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.97 (s, 1H), 4.86 (td, J = 10.6, 4.5 Hz, 1H), 3.43−3.23 (m, 2H), 2.69 (ddd, J = 16.3, 11.3, 1.5 Hz, 1H), 2.42−1.99 (m, 4H), 1.96 (s, 3H), 1.87 (s, 3H), 1.84−1.12 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 190.4, 166.5, 163.9, 155.3, 127.2, 122.7, 72.9, 54.7, 53.1, 41.8, 32.7, 31.7, 29.0, 25.4, 24.8, 24.5, 22.0, 14.5; HRMS (ESI) calcd for $C_{19}H_{27}O_4^+$ $[M + H]^+$ 319.1909, obsd 319.1919.

*Compound **37S**:* IR (thin film, cm^{-1}) 2929, 2858, 1733, 1689, 1618, 1453, 1261, 1009, 859; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.95 (s, 1H), 4.93 (td, J = 10.6, 4.5 Hz, 1H), 3.31 (s, 2H), 2.32 (t, J = 5.7 Hz, 2H), 2.11 (s, 3H), 2.09 (s, 3H), 2.22−1.93 (m, 6H), 1.88−1.64 (m, 3H), 1.46−1.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 190.3, 167.0, 162.1, 157.7, 125.1, 122.9, 74.6, 55.7, 53.9, 52.4, 40.7, 40.2, 31.8, 30.7, 25.2, 24.5, 21.0, 18.7; HRMS (ESI) calcd for $C_{19}H_{27}O_4^+$ $[M + H]^+$ 319.1909, obsd 319.1898.

(4a*S*,8a*S*,12a*R*,12b*S*,12c*R*)-7-Hydroxy-8a,12b-dimethyl-2,3,4,4a,8a,9,10,11,12b,12c-decahydro-1*H*-naphtho[2,1-*c*]-chromene-6,12(8*H*,12a*H*)-dione (37S1). To a solution of TBAF (1 M in THF, 98 μL, 0.098 mmol) in THF (1.0 mL) was added lactone **37S** (16.2 mg, 0.051 mmol) in THF (1.4 mL) at −78 °C via a cannula, which was further rinsed with DMF (2.2 mL). The reaction was allowed to 0 °C and stirred for 2 h before it was quenched with satd aq NH_4Cl (1.0 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate = 2/1) to give polycyclic compound **37S1** (11 mg, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.95 (s, 1H), 4.23 (td, J = 10.7, 4.1 Hz, 1H), 2.55−2.43 (m, 1H), 2.38 (m, 3H), 2.31 (s, 1H), 2.21 (m, 1H), 2.08−1.82 (m, 2H), 1.82−1.66 (m, 4H), 1.44 (s, 3H), 1.42−1.16 (m, 6H), 1.16−1.03 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 171.2, 167.7, 104.6, 79.5, 59.6, 52.8, 44.8, 44.4, 43.6, 40.0, 36.9, 33.4, 27.9, 25.7, 24.0, 23.7, 23.2, 18.6; HRMS (ESI) calcd for $C_{20}H_{29}O_5^+$ $[M + H]^+$ 349.2015, found 349.2022.

(*Z*)-Ethyl 4-Allyl-3-methylhepta-2,6-dienoate (39). To an ice-cold suspension of sodium hydride (0.86 g, 0.021 mol) in DMF (12 mL) was added a solution of β-keto ester **38** (3.0 g, 0.014 mol) in DMF (12 mL). The mixture was slowly warmed to room temperature and stirred for 30 min before it was cooled back to 0 °C. A solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (6.0 g, 0.017 mol) in DMF (14 mL) was added dropwise, and the mixture was stirred at the same temperature for 3 h. The reaction was quenched with 10% aq citric acid (38 mL) and extracted with diethyl ether (30 mL × 2). The combined organic phase was washed with brine (10 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified with column chromatography (silica gel, hexanes/ethyl acetoacetate = 30/1) to give recovered **38** (1.4 g) and vinyl triflate **38S** (2.1 g, 45% or 85% based on recovered starting material) as light yellow solid: IR (thin film, cm^{-1}) 3082, 2988, 2931, 1726, 1658, 1415, 1380, 1217, 1140, 1030, 850; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J = 0.5 Hz, 1H), 5.72 (ddt, J = 17.0, 10.1, 7.1 Hz, 2H), 5.20−4.93 (m, 4H), 4.20 (qd, J = 7.1, 0.6 Hz, 2H), 4.12−3.92 (m, 1H), 2.41−2.13 (m, 4H), 1.30 (td, J = 7.1, 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 164.1, 134.3, 117.7, 111.4, 77.2, 61.1, 39.7, 35.8, 14.1; HRMS (ESI) calcd for $C_{13}H_{18}F_3O_5S^+$ $[M + H]^+$ 343.0827, obsd 343.0829.

To a stirred solution of vinyl triflate **38S** (1.9 g, 5.6 mmol) in THF (56 mL) were added *N*-methyl-2-pyrrolidone (3.5 mL, 36.7 mmol) and iron(III) acetylacetonate (0.10 g, 0.28 mmol) at −40 °C. A solution of methylmagnesium bromide in diethyl ether (3 M, 5.6 mL, 16.8 mmol)) was added dropwise while the temperature was maintained at −30 to −40 °C. The reaction was stirred for another 30 min before it was quenched with satd aq NH_4Cl and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetoacetate = 15/1) to give ester **39** (1.08 g, 93%): IR (thin film, cm^{-1}) 3079, 2982, 1714, 1643, 1439, 1377, 1193, 1149, 048, 992, 912, 856; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89−5.54 (m, 3H), 5.17−4.79 (m, 4H), 4.28−3.97 (m, 3H), 2.36−2.17 (m, 2H), 2.17−2.00 (m, 2H), 1.75 (d, J = 1.3 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 161.0, 136.5, 118.1, 115.8, 59.4, 39.0, 37.4, 19.4, 14.3; HRMS (ESI) calcd for $C_{13}H_{20}O_2^+$ $[M + Li]^+$ 215.1623, obsd 215.1631.

(*Z*)-Ethyl 3-Methyl-6-oxo-4-(2-oxopropyl)hept-2-enoate (40). To a stirred solution of ester **39** (6.08 g, 29 mmol) in DMF-H_2O (350 mL/50 mL) were added $PdCl_2$ (1.04 g, 5.8 mmol) and CuCl (5.78 g, 58 mmol). The mixture was stirred at room temperature under an atmosphere of oxygen overnight. The mixture was extracted with ethyl acetate (4 × 100 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 2/1) to give 2,6-diketone **40** (2.57 g, 36%) as light yellow solid: IR (thin film, cm^{-1}) 2985, 1712, 1643, 1362, 1149, 1034, 859; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 1H), 4.58 (p, J = 7.2 Hz, 1H), 4.20−3.93 (m, 2H), 2.51 (qd, J = 15.9, 7.2 Hz, 4H), 2.08 (s, 6H), 1.73 (s, 3H), 1.30−1.09 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 165.7, 158.9, 117.9, 59.7, 46.5, 32.1, 29.6, 20.7, 14.1; HRMS (ESI) calcd for $C_{13}H_{21}O_4^+$ $[M + H]^+$ 241.1440, obsd 241.1429.

(*R*,*Z*)-Ethyl 3-(3-Methyl-5-oxocyclohex-3-en-1-yl)but-2-enoate (42). To a stirred solution of amine **41** (0.65 g, 2.0 mmol) in toluene (40 mL) was added acetic acid (1.15 mL, 200 mmol) dropwise at room temperature. The resulting solution was cooled to −15 °C, and a solution of 2,6-diketone **40** (2.22 g, 9.2 mmol) in toluene (61 mL) was added via a cannular. Once the addition was

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complete, the reaction mixture was warmed to 0 °C and maintained at this temperature for 48 h before it was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 2/1) to give cyclohexenone **42** (1.8 g, 88%) as light yellow solid: IR (thin film, cm^{-1}) 2982, 1712, 1664, 1442, 1383, 1208, 1155, 1039; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (d, J = 0.9 Hz, 1H), 5.70 (d, J = 0.8 Hz, 1H), 4.49−4.31 (m, 1H), 4.21−3.98 (m, 2H), 2.42−2.28 (m, 3H), 2.24 (dd, J = 17.8, 4.8 Hz, 1H), 1.95 (s, 3H), 1.85 (d, J = 1.4 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 161.6, 158.5, 151.3, 126.2, 118.0, 59.7, 40.3, 36.0, 34.8, 24.3, 20.6, 14.2; HRMS (ESI) calcd for $C_{13}H_{19}O_3^+$ $[M + H]^+$ 223.1334, obsd 223.1330.

(*R*,*Z*)-3-(3-Methyl-5-oxocyclohex-3-en-1-yl)but-2-enal (42S). To a stirred solution of cyclohexenone **42** (122 mg, 0.55 mmol) in THF (5 mL) was added dropwise a solution of DIBAL-H in hexanes (1 M, 2.7 mL, 2.7 mmol) at −78 °C and the mixture stirred for 4 h. The reaction was quenched with $Na_2SO_4{\cdot}10H_2O$, and the mixture was warmed to room temperature. The resulting suspension was cleared by filtration through a pad of Celite with ethyl acetate (150 mL). The filtrate was dried over anhydrous $MgSO_4$ and filtered. After concentrated *in vacuo*, the reaction crude was used without further purification.

To a solution of CrO_3 (823 mg, 8.23 mmol) in dichloromethane was added pyridine (1.33 mL, 16.5 mmol) in 5 min at 0 °C. The resulting mixture was warmed to room temperature and stirred for 15 min before it was cooled back to 0 °C. To this mixture was added the above reaction crude as a solution in dichloromethane (1.77 mL) by cannular transfer. The mixture stirred for 15 min before silica gel (5 g) was added. The dispersed solid was quickly filtered through a pad of Celite with ethyl acetate. The filtrate was combined and concentrated, and the residue was purified with column chromatography to give aldehyde **42S** (50 mg, 51% over two steps) as colorless solid and its geometric isomer due to isomerization of the enal alkene (10 mg): IR (thin film, cm^{-1}) 2978, 2916, 1667, 1628, 1377, 1190, 1111, 1022; ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (d, J = 7.6 Hz, 1H), 6.06−5.82 (m, 2H), 4.06 (ddd, J = 16.9, 11.9, 4.8 Hz, 1H), 2.66−2.33 (m, 3H), 2.24 (dd, J = 17.9, 4.0 Hz, 1H), 2.02 (s, 3H), 2.00−1.94 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 189.1, 161.9, 160.9, 129.2, 126.3, 40.6, 36.4, 35.3, 24.2, 20.5; HRMS (ESI) calcd for $C_{11}H_{15}O_2^+$ $[M + H]^+$ 179.1072, obsd 179.1077.

(*R*,*Z*)-Ethyl 5-(3-Methyl-5-oxocyclohex-3-en-1-yl)-3-oxohex-4-enoate (43). To a stirred solution of aldehyde **42S** (549 mg, 3.08 mmol) and ethyl diazoacetate (0.96 mL, 9.24 mmol) in dichloromethane (4 mL) was added $SnCl_2$ (292 mg, 1.54 mmol). The mixture was stirred at 30 °C for 3 h before it was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate =2/1) to give β-keto ester **43** (464 mg, 57%) as a mixture of its keto and enol forms: IR (thin film, cm^{-1}) 2982, 2940, 2911, 1735, 1667, 1611, 1442, 1377, 1312, 1247, 1099, 1022, 891; ^1H NMR (300 MHz, $CDCl_3$) δ 12.27 (d, J = 1.5 Hz, 0.22H, enol form), 6.14 (s, 1H), 5.88 (s, 1H), 5.58 (s, 0.33H), 4.94 (s, 0.27H), 4.43−4.23 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.44 (s, 1.45H), 2.31 (ddd, J = 10.4, 8.7, 4.9 Hz, 4H), 1.96 (d, J = 2.7 Hz, 3H), 1.87 (dd, J = 12.7, 1.3 Hz, 3H), 1.41−1.04 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 191.6, 170.7, 167.4, 161.9, 161.5, 160.5, 126.2, 124.3, 121.6, 91.8, 61.3, 60.1, 50.7, 40.9, 40.1, 36.8, 36.5, 35.4, 34.7, 24.4, 24.3, 21.1, 14.2, 14.1; HRMS (ESI) calcd for $C_{15}H_{21}O_4^+$ $[M + H]^+$ 265.1440, obsd 265.1434.

4-(2-((4-Methoxybenzyl)oxy)ethyl)-5,6-dihydro-2*H*-pyran-2-one (44S1). A solution of 4-(2-hydroxyethyl)-5,6-dihydro-2*H*-pyran-2-one (**44S0**)[8] (3.02 g, 21 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (8.64 g, 30.6 mmol) in dichloromethane (42 mL) was treated with pyridinium 4-methylbenzenesulfonate (PPTS) (0.27 g, 1.1 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h before the second batch of 4-methoxybenzyl 2,2,2-trichloroacetimidate (2.0 g, 7.1 mmol) was added. The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate = 4/1) to give lactone **44S1** (3.94 g, 15 mmol, 71% or 82% based on recovered starting material) and recovered **44S0** (0.42 g): IR (thin film, cm^{-1}) 2902, 1720, 1613, 1510, 1466, 1250, 1223, 1083, 1030, 823; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 2H), 6.94−6.80 (m, 2H), 5.93−5.78 (m, 1H), 4.43 (s, 2H), 4.33 (t, J = 6.3 Hz, 2H), 3.79 (s, 3H), 3.61 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 6.1 Hz, 2H), 2.44−2.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 159.2, 159.0, 129.7, 129.3, 116.9, 113.8, 72.7, 66.5, 65.9, 55.2, 36.6, 28.0; HRMS (ESI) calcd for $C_{15}H_{19}O_4^+$ $[M + H]^+$ 263.1284, obsd 263.1277.

(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-3-(2-((4-methoxybenzyl)oxy)ethyl)-*N*-methylpent-2-enamide (44S3). To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (4.4 g, 45 mmol, azeotropically dried with toluene) in dichloromethane (50 mL) was added a solution of trimethylaluminum in toluene (2 M, 22.5 mL, 45 mmol) at 0 °C. The solution was allowed to room temperature and stirred for 2 h before it was cooled to 0 °C. A solution of lactone **44S1** (3.94 g, 15 mmol) in dichloromethane (20 mL) was cannulated in 20 min. The reaction was stirred for 1.5 h at the same temperature before it was quenched with $Na_2SO_4{\cdot}10H_2O$ (2 g) and warmed to room temperature. The mixture was filtered through a pad of silica gel and flushed with ethyl acetate. The filtrate was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified with silica gel column chromatography to give (*E*)-5-hydroxy-*N*-methoxy-3-(2-((4-methoxybenzyl)oxy)ethyl)-*N*-methylpent-2-enamide **44S2** (4.06 g, 84%) as colorless oil: IR (thin film, cm^{-1}) 3387, 2934, 2863, 1649, 1611, 1513, 1463, 1247, 1176, 1096, 1034, 820; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.17 (m, 2H), 6.93−6.80 (m, 2H), 6.36 (s, 1H), 4.60 (t, J = 4.5 Hz, 1H), 4.44 (s, 2H), 3.88−3.70 (m, 5H), 3.69−3.50 (m, 5H), 3.21 (s, 3H), 2.80−2.61 (m, 2H), 2.50 (t, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 159.2, 153.7, 130.1, 129.5, 129.2, 118.6, 113.7, 72.7, 68.1, 61.4, 60.5, 55.2, 37.7, 35.4, 32.2; HRMS (ESI) calcd for $C_{17}H_{26}NO_5^+$ $[M + H]^+$ 324.1811, obsd 324.1817.

To a solution of amide **44S2** (2.9 g, 9.75 mmol) and *tert*-butyldimethyl chloride (1.9 g, 12.7 mmol) in dichloromethane (25 mL) was added imidazole (1 g, 14.6 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h before the reaction was quenched with satd aq sodium bicarbonate (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 4/1) to give amide **44S3** (3.9 g, 99%): IR (thin film, cm^{-1}) 2955, 2934, 2860, 1655, 1632, 1614, 1513, 1463, 1247, 1176, 1093, 835; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.16 (m, 2H), 6.96−6.76 (m, 2H), 6.22 (s, 1H), 4.44 (s, 2H), 3.88−3.73 (m, 5H), 3.68−3.52 (m, 5H), 3.18 (s, 3H), 2.78 (t, J = 6.5 Hz, 2H), 2.54 (t, J = 6.6 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 159.1, 154.9, 130.3, 129.2, 116.3, 113.7, 72.6, 68.1, 62.9, 61.3, 55.2, 39.6, 35.6, 32.2, 25.9, 18.2, −5.4; HRMS (ESI) calcd for $C_{23}H_{40}NO_5Si^+$ $[M + H]^+$ 438.2676, obsd 438.2682.

(*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-4-(2-((4-methoxybenzyl)-oxy)ethyl)hex-3-en-2-one (44S4). A solution of amide **44S3** (3.3 g, 7.5 mmol) in THF (75 mL) was treated with a solution of methylmagnesium bromide in diethyl ether (3 M, 5.5 mL, 16.6 mmol) dropwise at 0 °C. The mixture was stirred for 1 h before the reaction was quenched with satd aq NH_4Cl, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and purified by column chromatography (silica gel, hexane/EtOAc = 4/1) to give methyl ketone **44S4** (2.9 g, 98%): IR (thin film, cm^{-1}) 2956, 2931, 2857, 1688, 1614, 1513, 1465, 1250, 1093, 832; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.20 (m, 2H), 6.93−6.83 (m, 2H), 6.13 (s, 1H), 4.44 (s, 2H), 3.81 (d, J = 1.9 Hz, 3H), 3.75 (t, J = 6.5 Hz, 2H), 3.58 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 6.5 Hz, 2H), 2.50 (td, J = 6.5, 1.0 Hz, 2H), 2.16 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 159.2, 157.2, 130.2, 129.3, 125.3, 113.8, 72.6, 67.5, 62.5, 55.3, 39.8, 35.9, 31.9, 25.9, 18.3, −5.4; HRMS (ESI) calcd for $C_{22}H_{37}O_4Si^+$ $[M + H]^+$ 393.2461, obsd 393.2452.

(*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-4-(2-((4-methoxybenzyl)oxy)ethyl)hex-3-en-2-one (44). To an ice cold solution of ketone **44S4** (285 mg, 0.73 mmol) in dichloromethane was added triethylamine (0.25 mL, 1.45 mmol). The mixture was treated with

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tert-butyldimethyl triflate (0.2 mL, 0.87 mmol) dropwise and stirred at the same temperature for 2 h. The reaction was quenched with satd aq sodium bicarbonate (10 mL) and extracted with diethyl ether. The combined organic phase was washed with brine, dried with anhydrous $MgSO_4$, and concentrated. The reaction crude was coevaporated with toluene and the residue was taken into THF (3.6 mL). The solution was cooled to −78 °C and treated with sodium bicarbonate (73 mg, 0.87 mmol) and NIS (210 mg, 0.93 mmol) in portions under N_2. The mixture was stirred at the same temperature for 1 h before it was quenched with satd aq sodium bisulfate (5 mL). The mixture was warmed to room temperature and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 4/1) to give iodide **44** (367 mg, 98%): IR (thin film, cm^{-1}) 2955, 2931, 2857, 1682, 1611, 1513, 1469, 1244, 1093, 832; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.87 (m, 2H), 6.26 (s, 1H), 4.44 (s, 2H), 3.84−3.68 (m, 7H), 3.60 (t, J = 6.4 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.57 (t, J = 6.3 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 161.9, 159.1, 130.0, 129.2, 121.2, 113.6, 72.5, 67.2, 62.3, 55.1, 40.0, 36.1, 25.8, 18.1, 8.5, −5.5; HRMS (ESI) calcd for $C_{22}H_{35}ILiO_4Si^+$ $[M + Li]^+$ 525.1509, obsd 525.1492.

(*Z*)-Ethyl 5-((1*R*,6*S*)-6-((*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-4-(2-((4-methoxybenzyl)oxy)ethyl)-2-oxohex-3-en-1-yl)-3-methyl-5-oxocyclohex-3-en-1-yl)-3-oxohex-4-enoate (45). To a freshly prepared solution of LDA in THF (0.515 M, 7.5 mL, 3.85 mmol) was cannulated a solution of β-keto ester **43** (484 mg, 1.8 mmol) in THF (36 mL) at −78 °C. The solution was stirred at the same temperature for 30 min before HMPA (1.6 mL, 9.2 mmol) was added. The solution was stirred for another 20 min before it was treated with a solution of iodide **44** (1.14 g, 2.2 mmol) in THF (12 mL) rapidly. The reaction mixture was stirred for 30 min, quenched with satd aq NH_4Cl (5 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 4/1 to 2/1) to give **45** (640 mg, 53%): IR (thin film, cm^{-1}) 2956, 2931, 2857, 1741, 1685, 1670, 1614, 1513, 1377, 1303, 1250, 1093; ^1H NMR (300 MHz, $CDCl_3$) δ 12.28 (s, 0.17H, enol form), 7.25 (m, 2H), 6.87 (m, 2H), 6.13 (s, 2H), 5.87 (s, 1H), 5.60 (s, 0.25H), 4.94 (s, 0.21H), 4.44 (s, 2H), 4.38−4.24 (m, 1H), 4.19 (qd, J = 7.1, 2.1 Hz, 2H), 3.80 (s, 3H), 3.74 (t, J = 6.6 Hz, 2H), 3.58 (td, J = 6.7, 2.8 Hz, 2H), 3.43 (s, 1.4H), 3.20−3.01 (m, 1H), 2.86 (ddd, J = 17.2, 7.7, 5.4 Hz, 1H), 2.74 (t, J = 6.5 Hz, 2H), 2.49 (dd, J = 20.0, 13.0 Hz, 3H), 2.29−2.14 (m, 1H), 2.08 (dd, J = 17.1, 3.3 Hz, 1H), 1.96 (s, 0.83H), 1.94 (s, 2.1H), 1.89 (s, 2.1H), 1.83 (s, 0.91H), 1.36−1.17 (m,3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 198.3, 192.0, 167.3, 159.9, 159.5, 159.2, 156.9, 130.3, 129.3, 126.2, 125.6, 125.3, 113.8, 72.6, 67.7, 62.8, 61.3, 55.3, 50.7, 44.2, 41.7, 40.5, 39.8, 36.2, 35.0, 26.0, 24.1, 20.3, 18.3, 14.1, −5.4; HRMS (ESI) calcd for $C_{37}H_{55}O_8Si^+$ $[M + H]^+$ 655.3666, obsd 655.3690.

(*Z*)-Ethyl 5-((1*R*,6*S*)-6-((*E*)-6-hydroxy-4-(2-((4-methoxybenzyl)oxy)ethyl)-2-oxohex-3 -en-1-yl)-3- methyl-5-oxocyclohex-3-en-1-yl)-3-oxohex-4-enoate (46). To a solution of TBAF in THF (1 M, 20 mL, 20 mmol) was added HF·Py (1.14 g) dropwise. After concentration *in vacuo*, the mixture was diluted with pyridine to a total volume of 25 mL. The solution was concentrated under reduced pressure until there was no change in mass.[30a]

To a stirred solution of **45** (170 mg, 0.26 mmol) in THF (8.5 mL) was added the HF-TBAF-Py solution (0.49 mL) prepared above and HF·Py (0.49 mL). The reaction mixture was stirred at room temperature for 1 h and treated with satd aq $NaHCO_3$ (10 mL). After being stirred for another 5 min, the mixture was extracted with EtOAc. The organic phase was washed with satd aq $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1/3) to provide alcohol **46** (20 mg, 14%) as light yellow oil: IR (thin film, cm^{-1}) 3464, 2934, 2869, 1738, 1682, 1664, 1610, 1513, 1442, 1380, 1303, 1247, 1096, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 12.28 (s, 0.1H, enol form), 7.25−7.18 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.22 (s, 1H), 6.14 (s, 1H), 5.88 (s, 1H), 5.62 (s, 0.2H), 4.94 (s, 0.1H), 4.50−4.37 (m, 2H), 4.37−4.25 (m, 1H), 4.25−4.10 (m, 2H), 3.89−3.73 (m, 5H), 3.67 (t, J = 6.1 Hz, 2H), 3.45 (s, 2H), 3.15−3.01 (m, 1H), 2.97−2.72 (m, 3H), 2.54−2.36 (m, 3H), 2.18 (td, J = 17.1, 4.1 Hz, 2H), 1.95 (s, 3H), 1.89 (s, 3H), 1.36−1.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 198.4, 192.0, 167.5, 160.2, 159.3, 159.2, 157.0, 130.1, 129.4, 126.6, 126.3, 125.6, 113.7, 72.7, 69.6, 61.4, 60.1, 55.2, 50.7, 44.4, 43.4, 41.8, 40.41, 34.9, 32.8, 24.1, 20.2, 14.2; HRMS (ESI) calcd for $C_{31}H_{40}O_8Li^+$ $[M + Li]^+$ 547.2883, obsd 547.2859.

(1*Z*,9*Z*,12a*S*,16a*R*)-9-(2-((4-Methoxybenzyl)oxy)ethyl)-1,15-dimethyl-7,8,12,12a,16,16a-hexahydro-3*H*-benzo[*g*][1]-oxacyclotetradecine-3,5,11,13(4*H*)-tetraone (47). A solution of alcohol **46** (14 mg, 0.026 mmol) in toluene (8.8 mL) was refluxed for 4.5 h before it was concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, hexane/ethyl acetate = 1/2) gave lactone **47** (4.0 mg, 31%) as colorless oil: IR (thin film, cm^{-1}) 2958, 2910, 2857, 1735, 1681, 1664, 1614, 1513, 1442, 1377, 1247, 1093, 1031, 820; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.08 (s, 1H), 5.97 (s, 1H), 5.95 (s, 1H), 4.63 (td, J = 11.5, 3.1 Hz, 1H), 4.51 (m, 1H), 4.41 (s, 2H), 4.18−4.01 (m, 1H), 3.80 (s, 3H), 3.69 (dt, J = 9.2, 5.8 Hz, 1H), 3.55 (td, J = 8.4, 5.8 Hz, 1H), 3.47 (d, J = 13.0 Hz, 1H), 3.25 (d, J = 13.0 Hz, 1H), 3.20 (d, J = 16.3 Hz, 1H), 3.10 (dt, J = 11.7, 5.7 Hz, 1H), 3.07−2.98 (m, 1H), 2.68 (dd, J = 17.2, 10.1 Hz, 1H), 2.55 (dd, J = 18.3, 7.9 Hz, 2H), 2.50−2.34 (m, 2H), 2.02 (dd, J = 17.7, 4.3 Hz, 1H), 1.96 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 198.0, 190.4, 166.7, 162.0, 160.4, 159.1, 154.0, 130.4, 129.3, 128.7, 125.9, 124.8, 113.7, 72.7, 69.6, 61.0, 55.3, 52.8, 45.6, 42.1, 41.4, 38.9, 34.2, 31.2, 24.3, 21.6; HRMS (ESI) calcd for $C_{29}H_{34}O_7Li^+$ $[M + Li]^+$ 501.2465, obsd 501.2479.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedure, list of additional compounds, and $^1H/^{13}C$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 881572−881575 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yang@mail.chem.tamu.edu.

Notes

The authors declare no competing financial interest.

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