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Cascade Cyclizations of Acyclic and Macrocyclic Alkynones: Studies toward the Synthesis of Phomactin A

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Abstract

A study of the reactivity and diastereoselectivity of the Lewis acid-promoted cascade cyclizations of both acyclic and macrocyclic alkynones is described. In these reactions, a β-iodoallenolate intermediate is generated via conjugate addition of iodide to an alkynone, followed by an intramolecular aldol reaction with a tethered aldehyde to afford a cyclohexenyl alcohol. The Lewis acid magnesium iodide (MgI_2) was found to promote irreversible ring closure, while cyclizations using $BF_3{\cdot}OEt_2$ as promoter occurred reversibly. For both acyclic and macrocyclic ynones, high diastereoselectivity was observed in the intramolecular aldol reaction. The MgI_2 protocol for cyclization was applied to the synthesis of advanced intermediates relevant to the synthesis of phomactin natural products, during which a novel transannular cation-olefin cyclization was observed. DFT calculations were conducted to analyze the mechanism of this unusual MgI_2-promoted process.

Introduction

Significant progress has been made in the development of new cyclizations and carbon-carbon bond forming reactions initiated by the conjugate addition of halide nucleophiles to different unsaturated carbonyl systems.[1] The variant involving the addition of iodide to alkynone derivatives, which generates β-iodoallenolate intermediates, was first described by Kishi in 1986. [2] Since then, β-iodoallenolates have proven to be versatile nucleophilic intermediates in reactions with aldehydes,[3] imines,[4] oxiranes,[5] and ketones.[3a-d] Asymmetric reactions have also been achieved using chiral Lewis acids[6] or chiral auxiliaries.[7] We have developed two related cascade cyclizations, promoted by two different Lewis acids, involving β-iodoallenolates **II** (Scheme 1).[8]

We proposed that treatment of alkynones **I** with titanium tetrachloride ($TiCl_4$) gave cyclohexenol products **IV** through chelated intermediates **III**, while treatment with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) led to intermediates of type **V**, which have rotational freedom to undergo oxa-Michael ring closure to produce oxacycles of type **VI**.

These cascades are some of the only examples of *intramolecular* reactions of β-iodoallenolates that have been reported,[9] despite their potential value as a method for the synthesis of highly functionalized ring systems. To effectively apply this reaction chemistry to problems in natural product synthesis, it will be important to develop an understanding of the factors governing diastereoselectivity in β-iodoallenolate cyclizations. In this article, we

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Supporting Information: Spectra (^1H and ^{13}C) of all new compounds, DFT computational details, X-ray crystallographic data for **9a** and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org/.

assess diastereoselectivity and reversibility in the cyclizations of both acyclic and macrocyclic β-iodoallenolates using different Lewis acid promoters. We have also applied this method to the synthesis of the ABD core of phomactin A, and observed an unexpected transannular cyclization that we analyzed using DFT calculations.

Results and Discussion

Cascade Cyclization Strategy for the Synthesis of the ABD Core of Phomactin A

Over the past few years, we have sought to implement this cascade cyclization in the preparation of oxadecalin **1**, which contains the ABD ring system of phomactin A and appropriate handles for further functionalization (Scheme 2).[8,10,11] The idea was to generate a β-iodoallenolate intermediate from macrocyclic alkynone **2**, which would undergo intramolecular aldol/oxa-Michael addition to deliver **1** via bicyclo[9.3.1]pentadecane **3**.

Macrocycle **2** was prepared as shown in Scheme 3.[10]

Intramolecular Nozaki-Hiyama-Kishi Cr(II)/Ni(II)coupling[12] followed by MnO_2 oxidation gave enone **5*Z*** in two steps from iodoalkyne **4**, along with isomeric enone **5*E*** (3.6 : 1 ratio of *Z* and *E* isomers). After chromatographic separation of the *E* and *Z*-isomers, both could be desilylated using a HF-pyridine solution in tetrahydrofuran. Oxidation of each primary alcohol with the Ley-Griffith reagent[13] afforded the alkynones **2** and **6**, respectively (Scheme 3).

Attempts to cyclize macrocyclic alkynone **2** with the usual promoters ($BF_3{\cdot}OEt_2$ and $TiCl_4$) were unsuccessful, producing complex mixtures of products. Since magnesium iodide (MgI_2) has been reported to promote β-iodoallenolate formation/ aldol reaction,[3g,3i,9] we next tried cyclizing **2** using MgI_2 (1.3 equiv) in dichloromethane. The reaction did not produce either cyclohexenyl alcohol **3** or oxadecalin **1**; instead, a 1:1 mixture of products was generated: cyclohexenyl alcohol **7** (isolated as a single diastereomer) and tricycles **8a/ 8b** (isolated as a 2.7:1 mixture of endo/ exo isomers; see Scheme 4, top).

We tried adding *n*-Bu_4NI (1.3-5 equiv) to the reaction mixture,[8] in an attempt to favor the formation of phomactin skeleton **7** over the tricyclic system **8**, but the ratio of **7** to **8** did not change. However, we were able to avoid the formation of tricycles **8** by changing the solvent: if the reaction was run in tetrahydrofuran instead of dichloromethane, cyclohexenyl alcohol **7** was produced as the sole product in 60% yield and as a single diastereomer (Scheme 4, bottom).

We converted the mixture of tricycles **8a** (*endo*) /**8b** (*exo*) into *p*-nitrobenzoyl esters **9a** (*endo*) /**9b** (*exo*), which enabled us to obtain X-ray crystal structures of both the *endo* and *exo* isomers.[14] The stereochemistry of the tricyclic system is shown in Scheme 4.

Since we needed cyclohexenyl **3** to assess the strategy outlined in Scheme 2, we performed a standard Mitsunobu inversion[25] on cyclohexenyl alcohol **7**, which furnished target **3** in 52% yield (Scheme 5). The oxa-Michael ring closure of **3** could be achieved under the standard conditions ($BF_3{\cdot}OEt_2$ at low temperature)[8] to afford target oxadecalin **1** in 20% yield.

To summarize, synthetic studies targeting phomactin revealed that macrocycles **2** and **3** exhibit unusual cyclization behavior. In particular: 1) MgI_2 was identified as a mild alternative to $BF_3{\cdot}OEt_2$ and $TiCl_4$, and optimal for promoting the β-iodoallenolate cyclization of acid-sensitive alkynone **2**; 2) the cyclization of **2** is highly diastereoselective; 3) tricycles **8** are produced unexpectedly from **2**, through an unknown mechanism and 4) the $BF_3{\cdot}OEt_2$-promoted oxa-Michael ring closure of cyclohexenyl alcohol **3** is inefficient. We

conducted further cyclization studies on both acyclic and macrocyclic systems to improve our understanding of these four experimental observations.

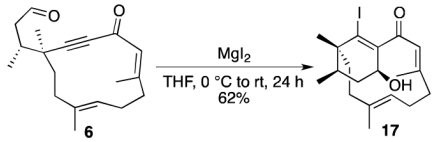
MgI_2-promoted cyclizations of acyclic and macrocyclic alkynones—Further experimentation with MgI2 as a promoter indicated that cyclization results were comparable to experiments employing TiCl4, producing cyclohexenols of type **IV** rather than oxadecalins of type **VI** (Scheme 1). Cyclization of **10** with $TiCl_4$ gives cyclohexenyl alcohol **11** in 82% yield (Table 1, entry 1), while MgI_2 produces **11** in 75% yield (entry 2). The analogous cyclization using $BF_3{\cdot}OEt_2$ produces **12** (entry 3). The observed reactivity is readily explained by chelation: like $TiCl_4$, MgI_2 is able to bind both oxygens of the aldol product (cf. **III**, Scheme 1), which prevents oxa-Michael ring closure.[8]

The two cyclization protocols were also successfully applied to the synthesis of β-bromocyclohexenyl alcohols. Cyclization of **10** using $MgBr_2$ as promoter generated **13** in moderate yield (entry 4).[15] Treatment of **10** with $BF_3{\cdot}OEt_2$/*n*-Bu_4NBr promoted the cascade cyclization to produce oxadecalin **14** in 46% yield (entry 5). In general, these reactions required longer reaction times and warmer temperatures compared to the cyclizations carried out with iodide as the nucleophile (cf. entry 2 vs. 4 and entry 3 vs. 5).

Finally, treatment of ketone **15** with MgI2 produced **16** in 78% yield (equation 1), whereas $TiCl_4$ and $BF_3{\cdot}OEt_2$ were not competent promoters.[16] This result further demonstrates that MgI_2 is a viable alternative to $TiCl_4$ and BF3·OEt2 for acid sensitive substrates, and it is also convenient that the MgI_2-promoted protocol does not require an external halide source (Table 1, entries 2 and 4, and equation 1).

(1)

In additional experiments on the macrocyclic phomactin system, we found that *E*-enone **6** could be cyclized upon treatment with MgI_2 in tetrahydrofuran, without isomerization of the α,β-unsaturated ketone. Cyclohexenyl alcohol **17** was obtained as a single diastereomer in 62% yield (equation 2).[17] Importantly, compound **17** represents an alternative intermediate useful for synthesis of the phomactin skeleton, as it contains the relevant bicyclo[9.3.1]pentadecane core.



(2)

Diastereoselectivity of the β-Iodoallenolate Aldol Cyclization—To explain why the intramolecular aldol cyclization of alkynone **2** selectively produces diastereoisomer **7** rather than **3**, it was helpful to perform a conformational analysis of β-iodoallenolate intermediates complexed with magnesium (Scheme 6). When macrocyclic alkynone **2** is

exposed to MgI_2, 1,4-addition of iodide is expected to produce two β-iodoallenolate diastereoisomers (**18** and **19**; Scheme 6). Cyclization of **18** via a Zimmerman-Traxler transition state is predicted to produce the major diastereoisomer **7**.[18,19] In contrast, β-iodoallenolate **18** (*axial*) is not aligned to form the magnesium chelate, while chelation of β-iodoallenolate **19** would produce two boat-like complexes, which may not form within the rigid macrocyclic system. Cyclization of **18** (*equatorial*) would deliver the observed cyclohexenol **7**. To account for the high isolated yield of **7**, it is reasonable to propose that β-iodoallenolate isomers **18** and **19** can equilibrate via reversible 1,4-addition of iodide,[20] allowing selective cyclization via chelate **18** (*equatorial*).

Cyclization studies on acyclic alkynone **20** provided further insight on the diastereoselectivity and reversibility of the intramolecular aldol reactions of β-iodoallenolate intermediates. Alkynone **20** was prepared as shown in Scheme 7. Selective mono-protection of the primary alcohol using *tert*-butyldimethylchlorosilane provided compound **22** in good yield. Then, oxidation of the neopentyl alcohol with Dess-Martin periodinane[21] followed by a one-carbon homologation using the Ohira-Bestmann reagent [22] afforded desired alkyne **23**. Then, addition of the lithium acetylide to aldehyde **24**[11g] and oxidation of the resulting allylic alcohol gave the desired ketone **25** in 61% yield over two steps. Deprotection followed by oxidation of the resulting alcohol gave alkynone **20**.

Cyclization of **20** with MgI_2 in dichloromethane provided cyclohexenyl alcohols **27** and **28** in 77% yield as a 10:1 mixture of diastereomers (Scheme 8).[23] This result is consistent with the model in Scheme 6, which predicts preferential formation of **27** through a magnesium chelate analogous to **18** (*equatorial*). The flexibility of the acyclic system must allow the intramolecular aldol reaction to occur through one of the axial conformations as well, resulting in formation of minor diastereomer **28**.

When pure samples of cyclohexenyl alcohol **27** and **28**[24,25] were treated with $BF_3{\cdot}OEt_2$ to promote the oxa-Michael reaction,[26] **27** afforded oxadecalin **29** in 90% yield, but the reaction of **28** did not produce any of the corresponding oxadecalin **30**. Instead, oxadecalin **29** was isolated in 30% yield (Scheme 9).

This result suggests that treatment of **28** with $BF_3{\cdot}OEt_2$ can lead to the formation of **27** (with only moderate efficiency), via the corresponding β-iodoallenolate intermediates. The high-yielding, diastereoselective oxa-Michael ring closure of **27** then produces **29** (Scheme 10). The fact that only one oxadecalin isomer was obtained (**29** and not **30**) indicates that cyclohexenol **28** must undergo retro-aldol reaction more readily than oxa-Michael ring closure. In contrast, no reaction occurred upon treatment of either cyclohexenyl alcohol **28** or cyclohexenyl alcohol **3** (see Scheme 5) with MgI_2. Taken together, these results suggest that intramolecular aldol reactions of β-iodoallenolate intermediates with $BF_3{\cdot}OEt_2$ can occur reversibly, while the analogous MgI_2-promoted cyclizations are irreversible.[20] Thus, the inability to achieve efficient oxa-Michael ring closure in both **28** and the phomactin system **3** (see Scheme 5) using $BF_3{\cdot}OEt_2$ may be attributed to a competing retro-aldol reaction. Fortunately, we were able to identify two other methods for inducing the oxa-Michael addition of **3**. These results are described in the next section.

Synthesis of the ABD Ring System of Phomactin—To advance the synthesis of phomactin A, we explored alternative strategies for obtaining oxadecalin **1** from cyclohexenyl alcohol **3**. Treatment with 10 mol% of $AuCl_3$ in dichloromethane at 0 °C effectively induced oxa-Michael addition, affording oxadecalin **1** in 50% yield,[26] or alternatively, exposure to *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine afforded silyl enol ether **31** in 54% yield (Scheme 11).[10] This sequence is particularly advantageous because the oxa-Michael addition occurs with

simultaneous protection of the ketone, providing a flexible intermediate that can be functionalized in different ways.

Mechanism of Formation of Tricycles 8a and 8b: DFT studies—The Lewis acid-promoted cyclization of **2** in dichloromethane resulted in significant production of tricycles **8** (see Scheme 4). Different reaction pathways can be proposed to rationalize this outcome. One possibility involves a cation-olefin cyclization cascade,[27] with concerted formation of two new bonds to generate intermediate **32**, followed by elimination to produce tricycles **8** (Scheme 12). Alternatively, stepwise mechanisms can be invoked, although these would require the formation of a high energy intermediate such as strained allene **33** or vinyl cation **34** (Scheme 12).

We performed DFT calculations to assess the feasibility of these different reaction pathways.[28,29] Although DFT is rarely used with magnesium,[30] it is the only reasonable computational method that can be used with such a large system. Because MgI_2 can decompose into several species in solution,[31] we modeled multiple promoters: MgI_2, $MgI_2{\cdot}2THF$, MgI^+, $MgI^+{\cdot}THF$, and Mg^{2+}. In each case, solvation corrections were obtained by the PCM method. We observed the systematic formation of a chelate as starting complex (see **B**, Table 2).

Its formation is weakly exothermic in CH_2Cl_2. In THF, it is moderately exothermic with MgI_2, MgI^+, or Mg^{2+}, appreciably exothermic with $MgI^+{\cdot}THF$, but strongly endothermic with $MgI_2{\cdot}2THF$ because of the steric strain.[32] The cyclization of the chelate gave rise to the tricyclic core **D** in a concerted fashion (cf. intermediate **32**, Scheme 11), via transition state **C**. The formation of the two rings is asynchronous, as shown by the very distinct values between ***d1*** and ***d2*** in **C** (Table 2), suggesting that **C** is more similar to **33** than to **34**.[33] Dissociation of the metallic fragment from **D** leads directly to the tricycle. In CH_2Cl_2, a reasonable free energy of activation was calculated with Mg^{2+}. On the other hand, $MgI^+{\cdot}THF$ gave rise to the lowest lying transition state in THF. All cyclizations were endothermic, but the decomplexation of the catalyst from **D** always proved exothermic. Overall, the cyclization of **A** into **E** liberates 26.6 kcal/mol of free energy. The subsequent isomerization of **E** into the observed product **8** presumably relieves strain in the tricyclic system.

Thus, DFT calculations support a Lewis acid-catalyzed cation-olefin cascade as the most reasonable reaction pathway for cyclization of **2** to **8**. To the best of our knowledge, this is a unique example of a reaction in which activation of an aldehyde triggers a tandem cyclization involving an electron-deficient alkyne and an alkene.[34] The transannular relationship of the alkyne and the alkene is probably an important factor. We did not make attempts to optimize the reaction to favor the formation of **8** over the desired target **7**, but further experimentation is planned to further evaluate this interesting cyclization.

Conclusion

In summary, these studies provide new insight into the reactivity and diastereoselectivity of the Lewis acid-promoted cyclizations of both acyclic and macrocyclic alkynones. Our experiments indicate that the 1,4-addition of iodide to an alkynone is a reversible process using either MgI_2 or $BF_3{\cdot}OEt_2$, and generates a β-iodoallenolate intermediate. This intermediate can then undergo an intramolecular aldol reaction with a tethered aldehyde to afford a cyclohexenyl alcohol. We present evidence that MgI_2 promotes irreversible ring closure, while the analogous $BF_3{\cdot}OEt_2$-promoted cyclization occurs reversibly. For both acyclic and macrocyclic ynones, we found that the aldol reaction is highly diastereoselective. The MgI_2 protocol was employed in the synthesis of a tricycle

corresponding to the ABD ring system of phomactin A. Finally, we examined an interesting transannular cyclization generated under the Lewis acidic conditions, and gained insight into the process using DFT calculations.

Experimental Section

General

Reactions were carried out in oven-dried glassware under an argon atmosphere. Reagents were used as obtained from commercial suppliers without further purification. ACS grade hexanes and ethyl acetate were used for column chromatography. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 glass-supported plates. Column chromatography was carried out on 60Å silica gel (230-400 mesh). Visualization on thin layer chromatography was done with a UV lamp followed by staining with either potassium permanganate/heat or *p*-anisaldehyde/heat. Infrared (IR) absorbance frequencies are given in cm^{-1} at the peak maximum. High resolution mass spectra were obtained a time-of-flight (TOF) mass spectrometer.

Spectroscopic Data

Structural assignment, including the identification of *E*/*Z* isomers and *cis*/*trans* isomers, was determined by either ^{1}H and ^{13}C NMR spectroscopy (at either 400 or 500 MHz and 100 or 125 MHz, respectively), and by nOe experiments and 2D COSY (when necessary), or an X-ray crystal structure. Chemical shifts are given in ppm, referenced to the residual proton resonance of the solvents (δ = 7.26 for $CHCl_3$, δ = 7.16 for C_6H_6) or to the residual carbon resonance of the solvent (δ = 77.1 for $CHCl_3$, δ = 128.0 for C_6H_6) Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, and t refer to multiplet, singlet, doublet, and triplet. In all cases, unless otherwise noted, the major diastereomer is reported.

Experimental conditions and spectral data for the preparation of the following compounds have been reported previously: **10** and **15**;[8] **4** and **21**.[10] Experimental details and spectral data for other compounds previously studied in our laboratories (**1**, **2**, **3**, **5*Z***, **5*E***, **7, 12, 14** and **31**)[8,10] are provided below.

General Procedure for β-Iodoallenolate Cyclizations Run with MgI_2

Magnesium iodide (at the indicated equivalents) was added to a stirred solution of the alkynone (1.0 equiv) in dry CH_2Cl_2 (0.10 M) or THF (0.10 M) at 0 °C. The reaction was then carried out at the indicated temperature and time. After completion of the reaction, the mixture was diluted with ethyl acetate, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate (3×). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution (2×), brine (1×), dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel using different gradients of hexanes and ethyl acetate to afford the pure products.

General Procedure for β-Iodoallenolate Cyclizations Run with $BF_3{\cdot}OEt_2$

Tetra-*n*-butylammonium iodide (at the indicated equivalents) was added to a stirred solution of the alkynone (1.0 equiv) in dry CH_2Cl_2 (0.10 M) at −40 °C. Boron trifluoride diethyl etherate (1.3 equiv) was then added dropwise. The reaction was carried out at the indicated temperature and time. After completion of the reaction, the mixture was diluted with ethyl acetate, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate (3×). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution (2×), brine (1×), dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash

chromatography on silica gel using different gradients of hexanes and ethyl acetate to afford the pure products.

(2*Z*,6*E*,10*S*,11*R*)-13-((*tert*-butyldimethylsilyl)oxy)-10-(iodoethynyl)-3,7,10,11-tetramethyltrideca-2,6-dienal (4):[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (d, *J* = 8.2 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 5.18 (t, *J* = 6.9 Hz, 1H), 3.77–3.69 (m, 1H), 3.66–3.60 (m, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.32–2.24 (m, 2H), 2.16–2.05 (m, 2H), 2.02 (s, 3H), 1.96–1.93 (m, 1H), 1.69–1.55 (m, 2H), 1.64 (s, 3H), 1.48–1.40 (m, 1H), 1.32–1.23 (m, 1H), 1.12 (s, 3H), 0.93 (s, 12H), 0.09 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.5, 163.7, 137.4, 128.5, 122.0, 100.7, 61.8, 40.9, 37.5, 36.9, 35.5, 34.6, 32.5, 27.0, 25.9, 25.0, 22.5, 18.2, 16.2, 13.9, −5.3. (1 carbon is missing due to overlap). **IR** (neat) 2949, 2926, 2854, 1669, 1631.

(*S*,2*Z*,6*E*)-10-((*R*)-4-((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-3,7,10-trimethylcyclododeca-2,6-dien-11-ynone (5*Z*) and (*S*,2*E*,6*E*)-10-((*R*)-4-((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-3,7,10-trimethylcyclododeca-2,6-dien-11-ynone (5*E*)

As described previously,[10] iodoalkyne **4** (295 mg, 0.556 mmol) was diluted in 6.3 mL of tetrahydrofuran, and slowly added, over 3 h, to a vigorously stirring solution of $CrCl_2$ (509 mg, 4.1 mmol) and $NiCl_2$ (0.07 mg, 0.055 mmol) in 44.8 mL of tetrahydrofuran. (NOTE: The tetrahydrofuran was thoroughly degassed (three times before each cyclization), and $CrCl_2$ was dried for at least 3 h at 180 °C under vacuum. All operations were carried out in the glove box, the addition of the iodoalkyne was carried out in the atmosphere.) After approximately 3 h, the reaction mixture was quenched with 10 mL of saturated NH_4Cl solution, extracted with diethyl ether (3 × 50 mL), washed with NaS_2O_3 (2 × 30 mL), H_2O (2 × 30 mL), brine (2 × 30 mL), dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 95:5) to give the macrocycle (142 mg, 63%) as an unidentified mixture of diastereomers with a complicated ^{1}H-NMR spectrum, and was carried on to the next step without further purification.

The macrocycle (600 mg, 1.48 mmol), from above, was diluted in 15 mL of CH_2Cl_2 and MnO_2 (2.50 g, 28.73 mmol) was added and rt. After 2 days, the reaction mixture was filtered over celite and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 99:1) to give the *Z*-ketone, (302 mg, 69%, traces of the *E*-isomer are present, only the *Z*-isomer is reported) as a yellow oil, and the *E*-ketone, (85 mg, 19%) as a yellow oil. The geometry of the *Z*-isomer was confirmed by nOe analysis (see supporting information). ***5Z***: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.84 (s, 1H), 5.47–5.39 (m, 1H), 3.74–3.66 (m, 1H), 3.65–3.58 (m, 1H), 2.61–2.46 (m, 2H), 2.27–2.15 (m, 4H), 2.00–1.91 (m, 1H), 1.88 (s, 3H), 1.86–1.75 (m, 2H), 1.66 (s, 3H), 1.51–1.43 (m, 1H), 1.30–1.20 (m, 1H), 1.18 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 180.3, 152.4, 134.3, 128.2, 125.4, 103.0, 84.6, 61.5, 38.2, 36.7, 35.2, 35.0, 32.1, 31.8, 25.9, 25.4, 24.0, 22.6, 18.2, 15.6, 13.7, −5.3 (2C). **IR** (neat) 2947, 2928, 2366, 2335, 2193, 1654, 1633, 1604. **HRMS** (ESI-TOF) *m/z* calculated for $C_{25}H_{42}O_2Si$ [M^+] 402.2954; found 402.2951.

5E

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.11 (t, *J* = 7.4 Hz, 1H), 3.72-3.62 (m, 1H), 3.61–3.54 (m, 1H), 2.37–2.19 (m, 4H), 2.09 (t, *J* = 6.1 Hz, 2H), 1.91–1.88 (m, 2H), 1.84 (s, 3H), 1.75–1.68 (m, 1H), 1.58–1.47 (m, 1H), 1.52 (s, 3H), 1.23–1.16 (m, 1H), 1.10 (s, 3H), 0.87 (s, 12H), 0.02 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 178.7, 147.6, 137.2, 132.3, 123.5, 106.6, 84.5, 61.4, 38.2, 37.6, 36.4, 35.3, 34.3, 33.1, 27.2, 25.9, 22.0, 18.2, 18.0, 14.8,

13.5, −5.3, −5.4. **IR** (neat) 2928, 2858, 2187, 1666, 1631, 1462, 1435, 1384, 1253, 1207, 1091. **HRMS** (ESI-TOF) *m/z* calculated for $C_{25}H_{42}O_2Si$ [M^+] 402.2954; found 402.2954.

(*R*)-3-((*S*,5*Z*,9*E*)-1,6,10-trimethyl-4-oxocyclododeca-5,9-dien-2-ynyl)butanal (2)

As described previously,[10] in a plastic reaction vessel, ***5Z*** (209 mg, 519 mmol) was dissolved in 4.2 mL of tetrahydrofuran and 0.42 mL of pyridine and cooled to 0 °C. Then, HF-pyridine (~70% HF in ~30% pyridine, 0.51 mL, 0.561 mmol) was slowly added. After 2 h, the reaction mixture was diluted in 2 mL of ethyl acetate and quenched with 10 mL of saturated solution of $NaHCO_3$. The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with 50 mL of saturated solution of $NaHCO_3$, 10 mL of saturated $CuSO_4$ solution, 20 mL of brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel to afford the primary alcohol (146 mg, 98%, traces of the *E*-isomer are present, only the *Z*-isomer is reported) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.48 (t, *J* = 7.9 Hz, 1H), 3.86–3.74 (m, 1H), 3.70–3.59 (m, 1H), 2.69–2.60 (m, 1H), 2.57–2.48 (m, 1H), 2.33–2.22 (m, 4H), 2.08–1.98 (m, 2H), 1.92 (s, 3H), 1.90–1.80 (m, 2H), 1.69 (s, 3H), 1.57–1.48 (m, 1H), 1.43–1.32 (m, 1H), 1.21 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 180.3, 153.3, 134.2, 128.1, 125.5, 103.2, 84.7, 61.2, 38.2, 37.4, 35.4, 35.1, 32.0, 31.9, 25.4, 24.1, 21.6, 15.5, 13.8. **IR** (neat) 3658–3090, 2973, 2939, 2874, 2195, 1627, 1600, 1442, 1377, 1348, 1280, 1249. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{28}O_2$ [M^+] 288.2089; found 288.2092.

The primary alcohol (227 mg, 0.788 mmol), from above, was stirred with 4-methylmorpholine *N*-oxide (138 mg, 1.18 mmol) and 4Å molecular sieves in 7.6 mL of dry CH_2Cl_2. After 20 min at rt, tetra-*n*-propylammonium perruthenate (14 mg, 0.04 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was quenched with 10 mL of saturated Na_2SO_3 solution, extracted with diethyl ether (3 × 20 mL), washed with brine, and saturated $CuSO_4$ solution. The combined organic layers were dried over $MgSO_4$, and filtered over celite. The resulting residue was concentrated to afford the aldehyde **2** (129 mg, 73%, traces of the *E*-isomer are present, only the *Z*-isomer is reported) as a yellow oil. The aldehyde was immediately used in the next reaction. (This compound was not stable to silica gel chromatography, but was sufficiently pure to use in the next step without further purification.)

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (s, 1H), 5.79 (s, 1H), 5.41 (t, *J* = 8.1 Hz, 1H), 2.84–2.75 (m, 1H), 2.54–2.44 (m, 1H), 2.34–2.24 (m, 2H), 2.24–2.14 (m, 4H), 1.84 (s, 3H), 1.79–1.69 (m, 1H), 1.61 (s, 3H), 1.59–1.44 (m, 2H), 1.14 (s, 3H), 0.91 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 201.6, 179.7, 153.2, 134.0, 128.1, 125.7, 101.0, 85.1, 47.4, 37.6, 35.0, 32.3, 32.0, 25.4, 24.1, 21.8, 15.5, 14.5 (1 carbon is missing due to overlap). **IR** (neat) 2966, 2935, 2877, 2854, 2198, 1724, 1627, 1600, 1466, 1377, 1280, 1249.

(*R*)-3-((*S*,5*E*,9*E*)-1,6,10-trimethyl-4-oxocyclododeca-5,9-dien-2-yn-1-yl)butanal (6)

In a plastic reaction vessel, ketone **5*E*** (201 mg, 500 mmol) was dissolved in 4.0 mL of tetrahydrofuran and 0.40 mL of pyridine and cooled to 0 °C. Then, 0.10 mL of HF-pyridine (~70% HF in ~30% pyridine) was slowly added. After 1 h, an additional 0.10 mL of HF-pyridine was added, and this process was repeated until completion of the reaction as indicated by TLC. (NOTE: If HF-pyridine is added rapidly or in one portion isomerization of the double bond will occur.) The reaction mixture was diluted in 2 mL of ethyl acetate and quenched with 10 mL of saturated solution of $NaHCO_3$. The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with

saturated $NaHCO_3$ solution, saturated $CuSO_4$ solution, brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 80:20) to give the alcohol (137 mg, 95%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (s, 1H), 5.10 (t, *J* = 7.3 Hz, 1H), 3.72–3.66 (m, 1H), 3.58–3.52 (m, 1H), 2.58 (bs, 1H), 2.37–2.24 (m, 3H), 2.23–2.13 (m, 2H), 2.12–2.05 (m, 2H), 1.92–1.86 (m, 3H), 1.82 (s, 3H), 1.72–1.62 (m, 1H), 1.50 (s, 1H), 1.47–1.45 (m, 1H), 1.29–1.19 (m, 1H), 1.09 (s, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 179.0, 148.2, 137.1, 132.1, 123.5, 106.6, 84.5, 61.1, 38.3, 37.6, 37.0, 35.3, 34.2, 33.1, 27.2, 21.5, 18.1, 14.8, 13.6. **IR** (neat): 3600–3045, 2974, 2931, 2858, 2719, 2191, 1730, 1675, 1637, 1450, 1343, 1275. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{29}O_2$ $[M+H]^+$, 289.4244; found 289.4248.

The above alcohol (137 mg, 0.475 mmol) was stirred with 4-methylmorpholine *N*-oxide (83 mg, 1.18 mmol) and 4Å molecular sieves in 7.6 mL of dry CH_2Cl_2. After 20 min at rt, tetra-*n*-propylammonium perruthenate (8.0 mg, 0.04 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was quenched with 10 mL of saturated Na_2SO_3 solution and extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine, saturated $CuSO_4$ solution, dried over $MgSO_4$, filtered over celite, and concentrated to give the aldehyde **6** (81 mg, 60%) as a yellow oil. (This compound was not stable to silica gel chromatography, but was sufficiently pure to use in the next step without further purification.)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 6.09 (s, 1H), 5.14 (t, *J* = 7.3 Hz, 1H), 2.77 (d, *J* = 13.8, 1H), 2.38–2.17 (m, 8H), 2.17–2.07 (m, 2H), 1.85 (s, 3H), 1.52 (s, 3H), 1.12 (s, 3H), 0.90 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 201.5, 178.4, 148.5, 136.1, 131.9, 123.8, 104.5, 85.1, 47.5, 37.8, 37.6, 34.6, 34.2, 33.5, 27.3, 21.4, 18.1, 14.8, 14.4. **IR** (neat): 2974, 2931, 2858, 2719, 2191, 1724, 1662, 1631, 1450, 1435, 1384, 1211. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{26}O_2$ $[M^+]$, 287.1933; found 287.1937.

(3*Z*,7*E*,11*S*,12*R*,14*S*)-14-hydroxy-15-iodo-4,8,11,12-tetra-methylbicyclo[9.3.1]pentadeca-1(15),3,7-trien-2-one (7)

As described previously,[10] compound **7** was prepared from alkynone **2** using the general protocol for the MgI_2-promoted cyclization. (Yield: 35 mg, 60%). (Eluent: hexanes:ethyl acetate, 90:10).

^{1}H NMR (500 MHz, C_6D_6): δ 6.39 (s, 1H), 5.18 (dd, *J* = 11.3 Hz, 4.6 Hz, 1H), 4.37–4.32 (m, 1H), 2.65 (d, *J* = 8.2 Hz, 1H), 2.40–2.33 (m, 1H), 2.19–2.12 (m, 1H), 2.10 (d, *J* = 13.7 Hz, 1H), 2.02–1.97 (m, 2H), 1.97–1.88 (m, 1H), 1.86–1.81 (m, 1H), 1.70 (s, 3H), 1.67–1.66 (m, 1H), 1.63–1.59 (m, 1H), 1.55 (d, *J* = 1.2 Hz, 3H), 1.30–1.21 (m, 1H), 1.11–1.07 (m, 1H), 0.88 (s, 3H), 0.70 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 200.5, 147.9, 142.5, 133.2, 128.7, 128.3, 125.7, 122.4, 70.4, 46.8, 36.8, 34.5, 33.5, 28.7, 24.8, 24.6, 21.8, 18.0, 17.4. **IR** (neat) 3631–3108, 2966, 2935, 2854, 1689, 1602, 1556, 1446, 1381. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{28}IO_2$ $[M+H]^+$, 415.1134; found 415.1146. $[\alpha]^{20}_D$ +82.9 (*c* 0.51, $CHCl_3$).

(3*Z*,7*E*,11*S*,12*R*,14*R*)-14-hydroxy-15-iodo-4,8,11,12-tetra-methylbicyclo[9.3.1]pentadeca-1(15),3,7-trien-2-one (3)

As described previously,[10] cyclohexenyl alcohol **7** (60 mg, 0.169 mmol) was dissolved in 1.34 mL of benzene and *p*-nitrobenzoic acid (442 mg, 1.69 mmol) and triphenylphosphine (282 mg, 1.69 mmol) were added. Then, diethyl azodicarboxylate (DEAD) (0.264 mL, 1.69 mmol) was slowly added to the reaction mixture at 0 °C. After completion of the reaction, as

indicated by TLC, the reaction mixture was quenched with 4 mL of saturated solution of $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with H_2O (1 × 4 mL), brine (1 × 4 mL), dried over $MgSO_4$, filtered over silica gel, and concentrated. The resulting residue was dissolved in 2 mL of methanol and K_2CO_3 (46 mg, 0.338 mmol) was added at 0 °C. The reaction mixture was warmed to rt. After 30 min, the reaction mixture was quenched with 4 mL of 1N HCl and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with H_2O (1 × 4 mL), brine (1 × 4 mL), dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 98:2 to hexanes:ethyl acetate 90:10 to hexanes:ethyl acetate 80:20) to afford the cyclohexenyl alcohol (31 mg, 52%) and the starting material (22 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 1H), 5.34–5.24 (m, 1H), 4.76 (s, 1H), 2.91–2.81 (m, 1H), 2.80–2.75 (m, 1H), 2.41 (t, *J* = 13.5, 1H), 2.31–2.17 (m, 3H), 2.04–2.01 (m, 1H), 1.96–1.86 (m, 2H), 1.85 (s, 3H), 1.80–1.62 (m, 2H), 1.73 (s, 3H), 1.51 (dd, *J* = 15.2, 3.2, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.1, 145.8, 143.2, 136.4, 131.9, 128.8, 127.4, 67.2, 47.5, 36.4, 35.7, 34.6, 32.0, 27.8, 24.4, 23.5, 23.4, 18.0, 17.3. **IR** (neat) 3640–3189, 1639, 1592, 1450, 1380, 1298, 1249. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{27}IO_2$ [M+Na$^+$], 437.0954; found 437.0954. $[\alpha]^{20}_D$ +298.7 (*c* 0.53, $CHCl_3$).

(1*R*,3*R*,3a*S*,6a*R,Z*)-1-hydroxy-3,3a,6,9-tetramethyl-2,3,3a,4,7,8-hexahydro-1*H*-cycloocta[*de*]naphthalen-11(6a*H*)-one (8a) and (3a*S*,4*R*,6*R*,11a*R,Z*)-6-hydroxy-3a,4,9-trimethyl-1-methylene-2,3,3a,4,5,6,11,11a-octahydro-1*H*-cycloocta[*de*]naphthalen-7(10*H*)-one (8b)

Compounds **8a** and **8b** were prepared from alkynone **2** using the general protocol for the MgI_2 promoted cyclization. Compounds **8a** (*endo*) and **8b** (*exo*) were obtained in a 2.7:1 ratio. (Yield: 10 mg, 23%). (Eluent: hexanes:ethyl acetate, 80:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.32 (s, 0.4H), 6.29 (s, 1H), 5.65 (d, *J* = 7.7 Hz, 1H), 4.98 (d, *J* = 7.4 Hz, 1H), 4.95 (d, *J* = 6.5 Hz, 0.4H), 4.89 (s, 0.4H), 4.80 (s, 0.4H), 3.46–3.39 (m, 0.4H), 3.28–3.18 (m, 1.4H), 3.17–3.10 (m, 1H), 2.68–2.46 (m, 1.1H), 2.38 (bs, 1H), 2.15–1.97 (m, 5.1H), 2.03 (s, 5.4H), 1.93–1.80 (m, 5.8H), 1.78 (s, 3.6H), 1.72–1.59 (m, 1.8 H), 0.96–0.92 (m, 5H), 0.88 (s, 1.2H), 0.08 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 196.5, 155.7, 155.4, 151.3, 150.9, 138.4, 137.7, 136.6, 132.8 (2C), 121.0, 110.0, 64.3, 44.0, 40.2, 40.0, 38.4, 36.5, 36.0, 35.1, 34.2, 33.7, 33.0, 32.3, 30.5, 30.1, 26.7, 26.3, 24.8, 21.6, 19.2, 17.4, 15.6, 15.4 (4 carbons are missing due to overlap). **IR** (neat): 3601–3202, 2950, 2923, 2872, 2815, 1730, 1636, 1603, 1554, 1484, 1452, 1435, 1376, 1298, 1258. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{26}O_2$ [M$^+$], 286.1927; found 286.1928.

(1*R*,3*R*,3a*S*,6a*R,Z*)-3,3a,6,9-tetramethyl-11-oxo-2,3,3a,4,6a,7,8,11-octahydro-1*H*-cycloocta[*de*]naphthalen-1-yl 4-nitrobenzoate (9a) and (1*R*,3*R*,3a*S*,6a*R,Z*)-3,3a,9-trimethyl-6-methylene-11-oxo-2,3,3a,4,5,6,6a,7,8,11-decahydro-1*H*-cycloocta[*de*]naphthalen-1-yl 4-nitrobenzoate (9b)

The **8a**/**8b** mixture from above (10 mg, 0.035 mmol) was stirred with *p*-nitrobenzoyl chloride (7 mg, 0.038 mmol) and pyridine (3.3 μL, 0.038 mmol) in 0.10 mL of CH_2Cl_2 at rt. After 1 h, the reaction mixture was quenched with 2 mL of 1 N HCl, extracted with diethyl ether (3 × 5 mL), washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The reaction mixture was purified by flash chromatography on silica gel (hexanes:ethyl acetate, 90:10 to 70:30) and, then, recrystallized from hexane to give *p*-nitrobenzoates **9a** and **9b** (8 mg, 53%; obtained in 2.4:1 ratio.)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.4 Hz, 6H), 8.03 (d, *J* = 8.3 Hz, 6H), 6.24–6.16 (m, 6.2H), 5.61 (d, *J* = 7.5 Hz, 2.1H), 4.83 (d, *J* = 4.1 Hz, 2H), 3.46–3.39 (m, 1H), 3.35–3.28 (m, 2.2H), 3.27–3.20 (m, 1.1H), 3.15–3.09 (m, 2.2H), 2.63–2.56 (m, 1H), 2.55–2.46 (m, 1.1H), 2.24–2.15 (m, 2H), 2.15–2.09 (m, 3H), 2.09–2.01 (m, 4.3H), 1.99–1.96 (m, 9.1H), 1.92–1.80 (m, 12.1H), 1.74 (s, 1H), 0.92–0.86 (m, 12.2H), 0.80 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ (**9a** (*endo*) is reported) 194.3, 163.6, 155.3, 153.0, 150.3, 132.3, 130.5, 123.4, 121.1, 70.4, 40.2, 39.7, 34.4, 33.9, 33.6, 32.2, 30.3, 26.4, 21.6, 21.6, 20.0, 15.2 (2 carbons are missing due to overlap). **IR** (neat): 2924, 2854, 1720, 1653, 1608, 1527, 1450, 1342, 1265, 1099, 1014. **HRMS** (ESI-TOF) *m/z* calculated for $C_{26}H_{29}NO_5$ [M+Na^+], 458.1943; found 458.1933.

4,4,9-trimethyl-7-oxodec-8-en-5-ynal (10).[8]

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H), 6.14 (s, 1H), 2.68 (t, *J* = 5 Hz, 2H), 2.23 (s, 3H), 1.96 (s, 3H), 1.84 (t, *J* = 5 Hz, 2H), 1.31 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 201.6, 176.7, 157.8, 126.2, 96.8, 83.6, 40.5, 34.4, 31.1, 28.3, 27.7, 21.1. **IR** (neat) 2970, 2924, 2854, 2206, 1724, 1651, 1608.

1-(6-hydroxy-2-iodo-3,3-dimethylcyclohex-1-en-1-yl)-3-methylbut-2-en-1-one (11)

Compound **11** was prepared from alkynone **10** using the general protocol for the MgI_2-promoted cyclization. (Yield: 526 mg, 82%). (Eluent: hexanes:ethyl acetate, 80:20). All spectral data for **11** were in agreement with published data.[8]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (s, 1H), 4.34 (m, 1H), 2.62 (s, 1H), 2.24 (s, 3H), 2.00 (s, 3H), 2.06-1.93 (m, 1H), 1.85-1.83 (m, 1H), 1.78-1.74 (m, 1H), 1.20 (s, 3H), 1.12 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 197.5, 158.4, 147.3, 123.7, 118.8, 68.0, 39.1, 32.6, 31.5, 29.0, 27.8, 21.3. **IR** (neat) 3623-3095, 2962, 2930, 2860, 1664, 1603. **HRMS** (ESI-TOF) *m/z* calculated for $C_{13}H_{19}O_2I_1Na$ [M+Na^+], 357.0321; found, 357.0322.

5-iodo-2,2,6,6-tetramethyl-6,7,8,8a-tetrahydro-2*H*-chromen-4(3*H*)-one (12)

As previously described,[8] compound **12** was prepared from alkynone **10** using the general protocol for the $BF_3{\cdot}OEt_2$-promoted cyclization. (Yield: 197 mg, 77%). (Eluent: hexanes:ethyl acetate, 90:10).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.48-4.45 (m, 1H), 2.63 (d, *J* = 15 Hz, 1H), 2.57 (d, *J* = 15 Hz, 1H), 2.08-2.02 (m, 1H), 1.95-1.91 (m, 1H), 1.87-1.83 (m, 1H), 1.72-1.66 (m, 1H), 1.34 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 199.7, 140.9, 121.6, 74.8, 71.7, 53.3, 41.3, 33.9, 30.6, 27.9, 26.5, 24.6. **IR** (neat) 2967, 2929, 2866, 1701, 1574. **HRMS** (ESI-TOF) *m/z* calculated for $C_{13}H_{19}O_2I_1$ [M^+], 334.0424; found 334.0423.

1-(2-bromo-6-hydroxy-3,3-dimethylcyclohex-1-en-1-yl)-3-methylbut-2-en-1-one (13)

Prepared from alkynone **10** using the general protocol for the MgI_2-promoted cyclization, except $MgBr_2$ was used, and the reaction was warmed to rt for 24 h. (Yield: 41 mg, 52%). (Eluent: hexanes:ethyl acetate, 80:20).

^{1}H NMR (400 MHz, C_6D_6): δ 6.30 (s, 1H), 4.33–4.30 (m, 1H), 2.69 (d, *J* = 4.1 Hz, 1H), 2.08 (s, 3H), 1.81–1.72 (m, 1H), 1.57–1.49 (m, 2H), 1.47 (s, 3H), 1.26–1.18 (m, 1H), 1.03 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (100 MHz, C_6D_6): δ 195.5, 156.3, 142.1, 135.8, 124.9, 68.2, 38.3, 34.0, 28.8, 27.6, 27.2, 26.9, 20.8. **IR** (neat) 3664–3140, 2966, 2935, 2866, 1666, 1608, 1442, 1381, 1238, 1168, 1067, 1041. **HRMS** (ESI-TOF) *m/z* calculated for $C_{13}H_{19}BrO_2$ [M+Na^+], 309.0466; found 309.0475.

5-bromo-2,2,6,6-tetramethyl-6,7,8,8a-tetrahydro-2*H*-chromen-4(3*H*)-one (14)

As described previously,[8] compound **14** was prepared from alkynone **10** using the general protocol for the $BF_3{\cdot}OEt_2$-promoted cyclization. (Yield: 35 mg, 46%). (Eluent: hexanes:ethyl acetate, 90:10).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.45-4.42 (m, 1H), 2.59 (d, *J* = 15 Hz, 1H), 2.53 (d, *J* = 15 Hz, 1H), 2.05-2.03 (m, 1H), 1.85-1.77 (m, 2H), 1.66-1.62 (m, 1H), 1.35 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 198.3, 139.0, 135.3, 74.7, 71.6, 53.9, 40.3, 35.1, 30.8, 30.5, 26.9, 26.3, 24.5. **IR** (neat) 2970, 2943, 2866, 1701, 1593. **HRMS** (ESI-TOF) *m/z* calculated for $C_{13}H_{19}O_2Br_1$ [M^+], 286.0563; found, 286.0567.

10-methylundec-9-en-6-yne-2,8-dione (15):[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (s, 1H), 2.58 (t, *J* = 8 Hz, 2H), 2.40 (t, *J* = 8 Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 1.86 (s, 3H), 1.85-1.80 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.7, 176.6, 157.8, 125.9, 91.1, 83.7, 41.9, 30.1, 27.8, 21.5, 21.1, 18.3. **IR** (neat) 2915, 2205, 1712, 1650, 1607.

1-(6-hydroxy-2-iodo-6-methylcyclohex-1-en-1-yl)-3-methylbut-2-en-1-one (16)

Prepared from alkynone **15** using the general protocol for the MgI_2-promoted cyclization. (Yield 40 mg, 78%). (Eluent: hexanes:ethyl acetate, 90:10). All spectral data for **16** were in agreement with published data.[8]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (s, 1H), 3.42 (bs, 1H), 2.79-2.75 (m, 1H), 2.70-2.63 (m, 1H), 2.26 (s, 3H), 2.01 (s, 3H), 1.92-1.91 (m, 1H), 1.89-1.88 (m, 1H), 1.69-1.62 (m, 2H), 1.32 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 198.1, 158.7, 149.6, 124.3, 100.1, 72.0, 41.5, 36.9, 28.5, 28.1, 21.7, 21.3. **IR** (neat) 3645, 3143, 2966, 2931, 2855, 1660, 1650, 1599. **HRMS** (ESI-TOF) *m/z* calculated for $C_{12}H_{17}O_2INa$ [M+Na^+], 343.0165; found, 343.0166.

(3*E*,7*E*,11*S*,12*R*,14*S*)-14-hydroxy-15-iodo-4,8,11,12-tetramethylbicyclo[9.3.1]pentadeca-1(15),3,7-trien-2-one (17)

Prepared from alkynone **6** using the general protocol for the MgI_2-promoted cyclization. (Yield: 49 mg, 62%). (Eluent: hexanes:ethyl acetate, 90:10). **^{1}H NMR** (400 MHz, C_6D_6): δ 6.11 (s, 1H), 4.89 (d, *J* = 9.7 Hz, 1H), 4.44–4.40 (m, 1H), 3.23 (bs, 1H), 2.34–2.18 (m, 1H), 2.07 (s, 3H), 1.99–1.86 (m, 4H), 1.83–1.70 (m, 4H), 1.66 (s, 3H), 1.47–1.38 (m, 1H), 1.20–1.09 (m, 1H), 0.86 (s, 3H), 0.75 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, C_6D_6): δ 196.2, 151.7, 148.6, 133.9, 126.9, 125.6, 119.3, 70.0, 46.2, 38.7, 36.3, 34.2, 33.9, 30.3, 26.6, 23.6, 18.9, 17.6, 17.5. **IR** (neat) 3608–3084, 2966, 2928, 2877, 2858, 1689, 1627, 1435, 1381, 1225, 1053. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{27}IO_2$ [M+Na^+], 437.0954; found 437.0953. $[\alpha]^{20}_D$ −7.8 (*c* 0.25, $CHCl_3$).

(2*S*,3*R*)-2,3-dimethyl-2-vinylpentane-1,5-diol (21)

As described previously,[10] an inseparable mixture of diastereomers (5.5:1) at the tertiary center was obtained. The mixture was carried on to the next step, and the ratio remained constant through all subsequent transformations. The major diastereomer is reported in all cases.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.21–5.05 (m, 2H), 3.83–3.75 (m, 1H), 3.67–3.60 (m, 1H), 3.59–3.38 (m, 2H), 2.45 (bs, 2H), 1.86–1.71 (m, 2H), 1.27–1.16 (m, 1H), 0.94 (s, 3H), 0.89 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.7, 114.4, 68.5, 61.5, 44.8, 33.8, 33.3, 15.3, 14.7. **IR** (neat) 3721–3027, 2962, 2877,

1728, 1635, 1454, 1415, 1377. **HRMS** (ESI-TOF) *m/z* calculated for $C_9H_{19}O_2$ $[M+H]^+$, 159.1385; found 159.1387.

(2*S*,3*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,3-dimethyl-2-vinylpentan-1-ol (22)

Diol **21** (4.2 g, 26.7 mmol) was diluted in 104 mL of CH_2Cl_2, cooled to 0 °C, and imidazole (4.3 g, 66.7 mmol) was added. After 20 min, *tert*-butyldimethylchlorosilane (4.2 g, 26.9 mmol) was slowly added to the reaction mixture at 0 °C. After 20 min, the reaction mixture was quenched with 30 mL of saturated NH_4Cl solution. The reaction mixture was then extracted with diethyl ether (3 × 50 mL), washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate, 90:10) to give the mono-protected alcohol (5.7 g, 80%, the major diastereomer is reported).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.15 (d, *J* = 10.9 Hz, 1H), 5.03 (d, *J* = 17.7, 1H), 3.74–3.68 (m, 1H), 3.60–3.46 (m, 2H), 3.42–3.35 (m, 1H), 1.94 (dd, *J* = 9.4, 3.9 Hz, 1H), 1.77–1.72 (m, 1H), 1.70–1.62 (m, 1H), 1.15–1.04 (m, 1H), 0.90 (s, 12H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.06 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.1, 114.0, 68.8, 62.1, 44.8, 34.1, 33.5, 25.9, 18.3, 15.0, 14.9, −5.3, −5.4. **IR** (neat): 3577–3130, 2954, 2927, 2882, 2856. **HRMS** (ESI-TOF) *m/z* calculated for $C_{15}H_{33}O_2Si$ $[M+H]^+$, 273.2250; found 273.2253.

tert-butyl(((3R,4S)-4-ethynyl-3,4-dimethylhex-5-en-1-yl)oxy)dimethylsilane (23)

Alcohol **22** (2.1 g, 7.7 mmol) was dissolved in 228 mL of CH_2Cl_2 and Dess-Martin periodinane[21] (4.2 g, 10.0 mmol) was added. After 15 min, the reaction mixture was diluted with 50 mL of CH_2Cl_2 and quenched with 80 mL of a saturated $NaHCO_3$ solution and 80 mL of a saturated $Na_2S_2O_3$ solution. After the solution became clear, the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered over a short pad of silica gel, and concentrated. The resulting residue was used in the next step without further purification.

The aldehyde (1.9 g, 1.0 mmol), from above, was stirred with K_2CO_3 (1.9 g, 14.0 mmol) in 32 mL of methanol. The Ohira-Bestmann reagent[22] (2.0 g, 10.5 mmol) was added at 0 °C. After 25 min, the reaction mixture was warmed to rt. After 24 h, the mixture was quenched with 10 mL of $NaHCO_3$ and extracted with hexanes (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The reaction mixture was purified by flash chromatography on silica gel (hexanes:ethyl acetate, 97:3) to give the alkyne (1.8 g, 95% over two steps, the major diastereomer is reported) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.40 (dd, *J* = 17.0 Hz, 1.5 Hz, 1H), 5.10 (dd, *J* = 10.2 Hz, 1.5 Hz, 1H), 3.70–3.64 (m, 1H), 3.61–3.54 (m, 1H), 2.26 (s, 1H), 1.89–1.79 (m, 1H), 1.60–1.49 (m, 1H), 1.27 (s, 3H), 1.27–1.14 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.4, 113.7, 86.9, 71.9, 61.6, 43.1, 38.1, 35.4, 25.9, 25.7, 18.2, 14.4, −5.3, −5.4. **IR** (neat): 3311, 2954, 2929, 2857, 2386. **HRMS** (ESI-TOF) *m/z* calculated for $C_{16}H_{30}OSi$ $[M^+]$, 266.2066; 266.2061.

(*E*)-3-methyloct-2-en-6-ynal (24)

(*E*)-3-methyloct-2-en-6-yn-1-ol[**Error! Bookmark not defined.**] (1.0 g, 7.2 mmol) was diluted in 66 mL of CH_2Cl_2, MnO_2 (12.6 g, 145.0 mmol) was added and the mixture was stirred at rt. After 2 d, the mixture was diluted with CH_2Cl_2, filtered over celite, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexane:ethyl acetate, 97:3) to give the aldehyde (800 mg, 80%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (d, *J* = 8.0 Hz, 1H), 5.92 (d, *J* = 8.0 Hz, 1H), 2.43–2.32 (m, 4H), 2.19 (s, 3H), 1.76 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.1, 161.7, 127.7, 77.0, 76.9, 39.4, 17.3, 16.8, 3.3. **IR** (neat): 2919, 2854, 1667, 1633, 1611. **HRMS** (ESI-TOF) *m/z* calculated for $C_9H_{12}O$ [M^+], 137.0602; found 137.0604.

(3*R*,4*S*,*E*)-1-((*tert*-butyldimethylsilyl)oxy)-3,4,9-trimethyl-4-vinyltetradeca-8-en-5,12-diyn-7-one (25)

Alkyne **23** (1.0 g, 3.7 mmol) was diluted in 11 mL of dry tetrahydrofuran and *n*-butyllithium (1.8 M in Hexanes 2.3 mL, 4.1 mmol) was slowly added at −78 °C. After 30 min, aldehyde **24** (6.13 mg, 4.5 mmol) was slowly added in 6.6 mL of tetrahydrofuran. After 3 h, the mixture was quenched with 10 mL of saturated NH_4Cl solution, and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered over a short pad of silica gel, and concentrated. The resulting residue was used in the next step without further purification.

The alcohol, from above, was diluted in 22 mL of CH_2Cl_2, MnO_2 (4.3 g, 49.7 mmol) was added and the mixture was stirred at rt. After 2 h, the mixture was diluted with CH_2Cl_2, filtered over celite, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate, 97:3) to give the ketone (924 mg, 61% over 2 steps, the major diastereomer is reported) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (s, 1H), 5.76 (dd, *J* = 17.1, 10.3 Hz, 1H), 5.36 (dd, *J* = 17.1, 1.0 Hz, 1H), 5.13 (dd, *J* = 10.2 Hz, 1.0 Hz, 1H), 3.72–3.62 (m, 1H), 3.62–3.53 (m, 1H), 2.32 (s, 4H), 2.19 (s, 3H), 1.90–1.79 (m, 1H), 1.76 (s, 3H), 1.72–1.60 (m, 1H), 1.32 (s, 3H), 1.28–1.17 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.7, 158.2, 141.2, 126.2, 114.4, 94.6, 86.8, 77.3, 76.7, 61.3, 43.5, 40.1, 38.3, 35.3, 25.8, 25.0, 19.4, 18.2, 17.2, 14.6, 3.3, −5.3, −5.4. **IR** (neat): 2951, 2927, 2855, 2206, 1654, 1651, 1608, 1384, 1360, 1255, 1220, 1125. **HRMS** (ESI-TOF) *m/z* calculated for $C_{25}H_{40}O_2Si$ [M^+], 400.2797; found 400.2806.

(3*R*,4*S*,*E*)-1-hydroxy-3,4,9-trimethyl-4-vinyltetradeca-8-en-5,12-diyn-7-one (26)

In a plastic reaction vessel, ketone **25** (220 mg, 550 mmol) was dissolved in 4.5 mL of tetrahydrofuran and 0.45 mL of pyridine and cooled to 0 °C. Then, HF-pyridine (~70% HF in ~30% pyridine, 0.54 mL, 0.594 mmol) was slowly added. After 2 h, the reaction mixture was diluted in 2 mL of ethyl acetate and quenched with 10 mL of saturated $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate (3 ×20 20 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution, a saturated $CuSO_4$ solution, brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel to give the alcohol (154 mg, 98%, the major diastereomer is reported) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (s, 1H), 5.72 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 3.81–3.73 (m, 1H), 3.68–3.60 (m, 1H), 2.42–2.35 (m, 4H), 2.24 (s, 3H), 1.99–1.89 (m, 1H), 1.81–1.78 (m, 2H), 1.80 (s, 3H), 1.76–1.69 (m, 1H), 1.37 (s, 3H), 1.06 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.7, 158.6, 141.1, 126.1, 114.6, 94.5, 61.0, 43.5, 40.1, 38.3, 35.3, 24.6, 19.5, 17.1, 14.5, 3.3 (3 carbons are missing due to overlap). **IR** (neat): 3678–3126, 2974, 2920, 2877, 2206, 1651, 1604, 1438, 1381, 1334, 1280, 1226, 1130. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{26}O_2$ [$M+Na^+$], 309.1831; found 309.1834.

(3*R*,4*S*,*E*)-3,4,9-trimethyl-7-oxo-4-vinyltetradeca-8-en-5,12-diynal (20)

Alcohol **26** (154 mg, 0.538 mmol) was stirred with 4-methylmorpholine *N*-oxide (94 mg, 0.807 mmol) and 4Å molecular sieves in 5.1 mL of dry CH_2Cl_2 at rt. After 20 min, tetra-*n*-propylammonium perruthenate (10 mg, 0.027 mmol) was added and the mixture was stirred for 2 h. The reaction was quenched with 10 mL of saturated Na_2SO_3 solution, extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, a saturated $CuSO_4$ solution, dried over $MgSO_4$, filtered over celite, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate, 90:10) to give the aldehyde (101 mg, 66%, the major diastereomer is reported) as a yellow oil. (Note: Purification of alkynone **20** was rapid, and it was not allowed to remain on silica gel for extended periods of time.)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 6.15 (s, 1H), 5.67 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.38 (d, *J* = 17.1, 1.0 Hz, 1H), 5.15 (d, *J* = 10.2 Hz, 1H), 2.67 (dd, *J* = 17.3, 2.9 Hz, 1H), 2.35–2.25 (m, 6H), 2.17 (s, 3H), 1.73 (s, 3H), 1.32 (s, 3H), 1.04 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 201.5, 176.3, 159.0, 140.8, 126.0, 115.4, 92.4, 87.5, 47.6, 43.2, 40.1, 36.1, 24.8, 19.5, 17.2, 15.5, 3.4 (2 carbons are missing due to overlap). **IR** (neat): 2974, 2920, 2854, 2723, 2210, 1774, 1724, 1651, 1604, 1442, 1441, 1381, 1338, 1280, 1222. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{25}O_2$ $[M+H]^+$, 285.1855; found 285.1865.

(*E*)-1-((3*S*,4*R*,6*S*)-6-hydroxy-2-iodo-3,4-dimethyl-3-vinylcyclohex-1-en-1-yl)-3-methyloct-2-en-6-yn-1-one (27)

Prepared from alkynone **20** using the general protocol for the MgI_2 promoted cyclization. (Yield: 23 mg, 77%). (Eluent: hexanes:ethyl acetate, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (s, 1H), 5.51 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.24 (d, *J* = 10.7 Hz, 1H), 5.04 (d, *J* = 17.3 Hz, 1H), 4.64–4.57 (m, 1H), 2.36 (s, 5H), 2.20 (s, 3H), 2.06–1.98 (m, 1H), 1.89–1.80 (m, 1H), 1.76 (s, 3H), 1.67–1.55 (m, 1H), 1.14 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.8, 159.0, 149.3, 145.8, 124.0, 114.9, 114.0, 77.6, 77.1, 70.2, 49.5, 40.4, 35.6, 35.4, 19.6, 18.0, 17.1, 16.6, 3.5. **IR** (neat) 3657–3126, 2966, 2920, 2874, 1666, 1608, 1446, 1411, 1377, 1320, 1176, 1141, 1060. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{25}IO_2$ $[M^+]$, 412.0899; found 412.0906.

(*E*)-1-((3*S*,4*R*,6*R*)-6-hydroxy-2-iodo-3,4-dimethyl-3-vinylcyclohex-1-en-1-yl)-3-methyloct-2-en-6-yn-1-one (28)

Cyclohexenyl alcohol **27** (30 mg, 0.072 mmol) was stirred with *p*-nitrobenzoic acid (60 mg, 0.363 mmol) and PPh_3 (95 mg, 0.363 mmol) in 0.72 mL of dry benzene. Then, diethyl azodicarboxylate (DEAD) (56 μL, 0.363 mmol) was slowly added to the reaction mixture at 0 °C. After 3 h at rt, the reaction mixture was quenched with 4 mL of saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered over a short pad of silica gel, and concentrated. The resulting residue was dissolved in 2.2 mL of methanol and K_2CO_3 (19 mg, 0.144 mmol) was added at 0 °C. The reaction mixture was warmed to rt. After 30 min, the reaction mixture was quenched with 4 mL of saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 98:2 to hexanes:ethyl acetate 90:10 to hexanes:ethyl acetate 80:20) to give the inverted cyclohexenyl alcohol (23 mg, 76% over 2 steps, the major isomer is reported).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (s, 1H), 5.63 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 5.12 (d, *J* = 17.3 Hz, 1H), 4.33 (s, 1H), 2.83–2.67 (m, 1H), 2.42 (s, 3H), 2.25

(s, 3H), 2.08 (d, *J* = 10.6 Hz, 1H), 1.90–1.69 (m, 6H), 1.10 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.4, 159.8, 147.1, 145.6, 123.565, 118.1, 115.0, 77.5, 67.2, 49.7, 40.4, 34.2, 32.2, 19.7, 17.6, 17.0, 15.8, 3.5 (1 carbon is missing due to overlap). **IR** (neat) 3720–3098, 2924, 2874, 2854, 1735, 1666, 1604, 1446, 1373, 1238, 1165. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{25}IO_2$ [M^+], 412.0899; found 412.0906.

(2*S*,6*S*,7*R*,8a*S*)-5-iodo-2,6,7-trimethyl-2-(pent-3-yn-1-yl)-6-vinyl-6,7,8,8a-tetrahydro-2*H*-chromen-4(3*H*)-one (29)

Prepared from cyclohexenyl alcohol **27** using the general protocol for the $BF_3{\cdot}OEt_2$-promoted cyclization. (Yield: 10 mg, 90%). (Eluent: hexanes:ethyl acetate, 95:5).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.51 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.29 (d, *J* = 12.9 Hz, 1H), 5.07 (d, *J* = 17.3 Hz, 1H), 4.51–4.46 (m, 1H), 2.60 (d, *J* = 2.8 Hz, 2H), 2.21–2.14 (m, 2H), 2.02–1.87 (m, 2H), 1.76 (s, 4H), 1.72–1.62 (m, 2H), 1.24 (s, 3H), 1.18 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 198.6, 145.2, 140.9, 119.8, 115.3, 78.3, 76.0, 75.9, 71.6, 52.5, 51.9, 36.4, 34.7, 33.0, 26.7, 18.1, 16.8, 12.8, 3.4. **IR** (neat) 2974, 2931, 2870, 1747, 1701, 1582, 1449, 1379, 1327, 1230, 1165. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{25}IO_2$ [M^+], 412.0899; found 412.0906.

Oxadecalin 1

Cyclohexenyl alcohol **3** (20 mg, 0.048 mmol) was diluted in 0.48 mL of dry CH_2Cl_2. $AuCl_3$ (1.4 mg, 0.004 mmol) was then added at 0 °C, and warmed to rt. After completion of the reaction by TLC, the reaction mixture was purified by flash chromatography on silica gel (hexane:ethyl acetate, 99:1) to afford the oxadecalin (10 mg, 50%) as a pale yellow oil. All spectral data for **1** were in agreement with published data.[10] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.51–5.44 (m, 1H), 4.16–4.11 (m, 1H), 3.06-2.94 (m, 1H), 2.78 (d, *J* = 17.1 Hz, 1H), 2.56 (d, *J* = 17.1 Hz, 1H), 2.47–2.32 (m, 2H), 2.08–1.95 (m, 3H), 1.87–1.76 (m, 1H), 1.75–1.41 (m, 4H), 1.66 (s, 3H), 1.29 (s, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.1, 143.5, 136.9, 130.5, 130.0, 76.1, 68.7, 48.7, 47.1, 41.6, 35.7, 35.0, 31.8, 29.7, 29.6, 26.1, 23.6, 23.5, 17.3. **IR** (neat) 2966, 2924, 2854, 1693, 1570, 1450, 1373, 1292, 1207, 1140, 1053. **HRMS** (ESI-TOF) *m/z* calculated for $C_{19}H_{27}IO_2$ [M^+], 415.1134; found 415.1137. $[\alpha]^{20}_D$ +200.4 (*c* 0.15, $CHCl_3$).

Tricycle 31

As described previously,[10] compound **3** (20 mg, 0.048 mmol) was dissolved in 0.5 mL of toluene at rt. Then, 2,6-lutidine (0.11 mL, 0.48 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (0.05 mL, 0.48 mmol) were rapidly added to the reaction mixture. After 10 min, the reaction mixture was diluted in 2 mL ethyl acetate, quenched with 0.5 mL of saturated NH_4Cl solution, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with H_2O (1 × 10 mL), brine (1 × 10 mL), dried of $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 98:2) to give the tricycle (15 mg, 54%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.41 (d, *J* = 8.5 Hz, 1H), 4.56 (s, 1H), 3.86 (t, *J* = 2.8 Hz, 1H), 2.97–2.83 (m, 1H), 2.36–2.18 (m, 3H), 2.01–1.86 (m, 3H), 1.75 (s, 3H), 1.67–1.157 (m, 4H), 1.23 (s, 3H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.99 (s, 9H), 0.89 (s, 3H), 0.22 (s, 3H), 0.19 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 150.2, 133.5, 131.3, 129.0, 120.4, 112.2, 77.9, 70.6, 46.2, 41.9, 35.8, 35.5, 32.3, 27.8, 26.4, 26.3, 24.8, 22.5, 19.5, 18.7, 17.5, −4.1, −4.3. **IR** (neat) 2958, 2928, 1635, 1462, 1323, 1253, 1200, 1085. **HRMS** (ESI-TOF) *m/z* calculated for $C_{25}H_{42}IO_2Si$ [M+H]$^+$, 529.1999; found 529.1990. $[\alpha]^{20}_D$ +21.3 (*c* 0.37, $CHCl_3$).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(16). Cyclization of **15** to **16** could also be promoted using $AlCl_3$ (6.5 equiv, 75% yield, see reference 8.)

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(23). Similarly, cyclization of alkynone **20** with MgI_2 in tetrahydrofuran gave cyclohexenyl alcohols **27** and **28** in 60% yield as a 7:1 mixture of diastereomers.

(24). Cyclohexenyl alcohols **27** and **28** were easily separated via flash chromatography, or alternatively, **28** could be obtained in 76% yield from cyclohexenyl alcohol 27 using standard Mitsunobu conditions.

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(29). Optimizations were carried out at the B3LYP/6-311G**[Mg,I]/6-31G*[other elements] level. Solvation corrections for dichloromethane and THF were carried out using the PCM method (UFF radii). Only the solvent corrected free energies are presented (kcal/mol).

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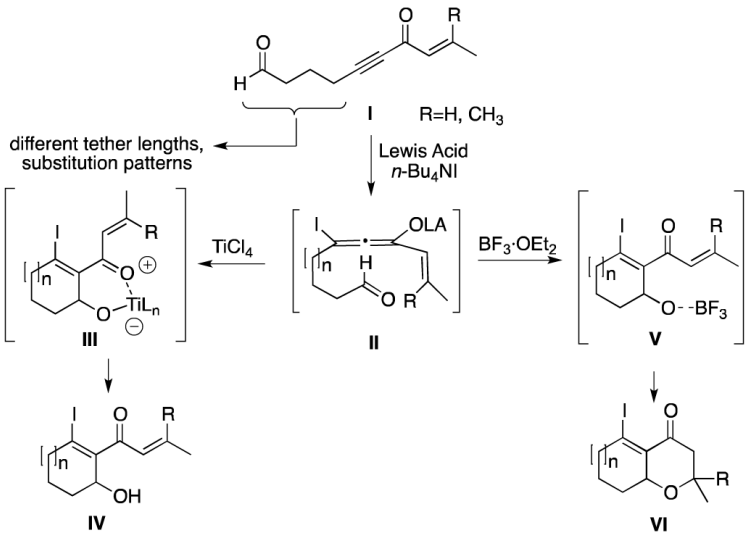
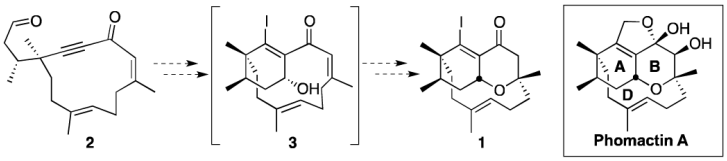
(32). See Supporting Information for the geometries.

(33). [**D**+MgI^+] is the only intermediate with a structure closely related to **33**. The distance between the central allene carbon and the aldehyde carbon is 2.54 Å, while the distance between the alkene carbon and the central allene carbon is 1.7 Å. However, dissociation of the metallic fragment directly leads to the cyclized product **E**.

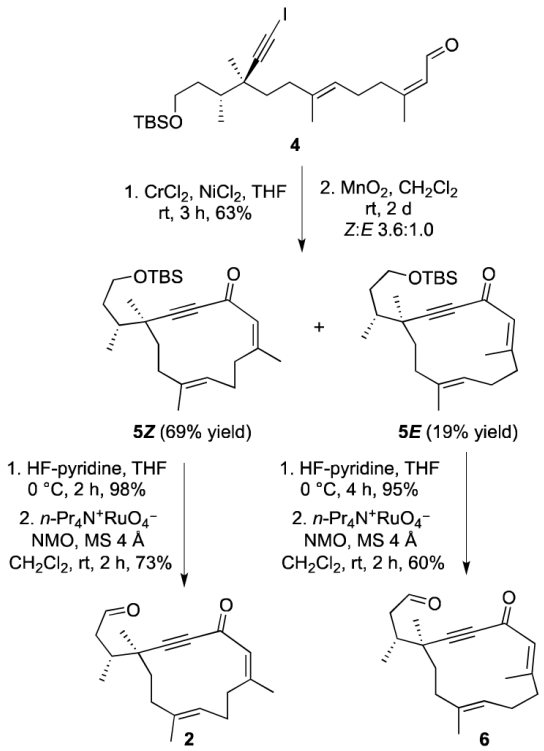
(34). In light of these findings, a concerted pathway must also be considered as a possible mechanism for the cyclization of type I alkynones into type IV β-iodocyclohexenyl alcohols (Scheme 1). By analogy, this cascade could be initiated by activation of the aldehyde with Lewis acid, which would suffer attack by the electron-deficient alkynone and intermolecular trapping with iodide. Studies are underway to assess the validity of this alternative mechanism.



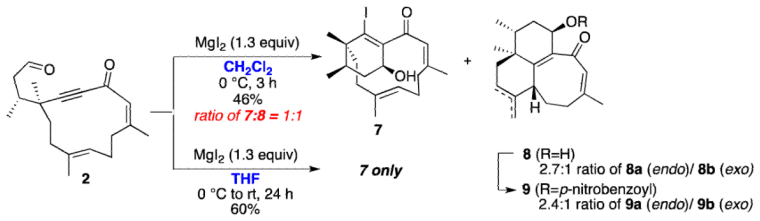
Scheme 1.
Lewis Acid-Initiated β-Iodoallenolate Cyclization.



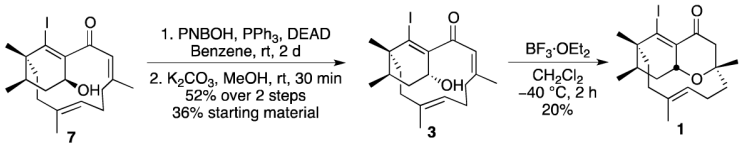
Scheme 2.
Strategy for the Synthesis of Phomactin A.



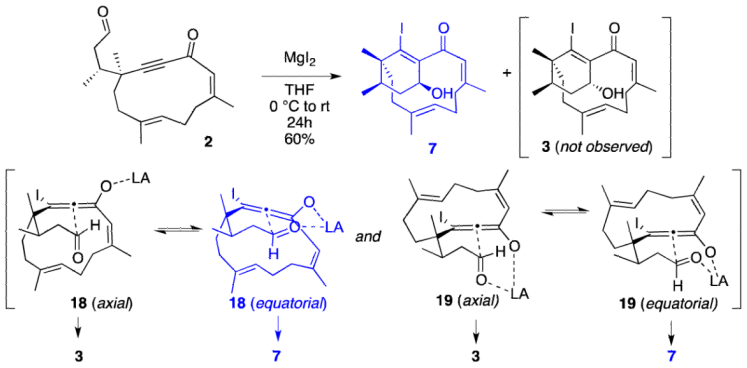
Scheme 3.
Synthesis of Macrocycles **2** and **6**



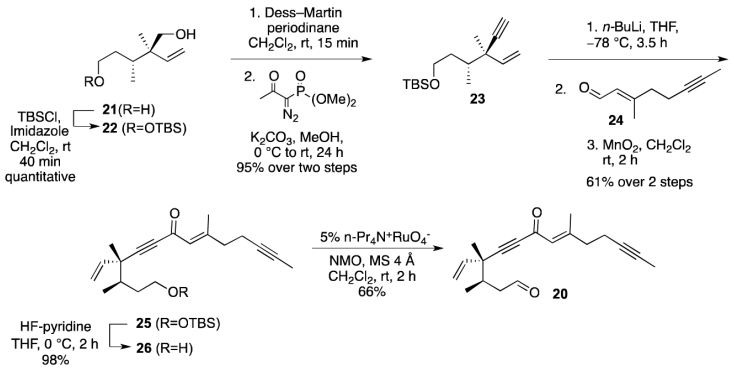
Scheme 4.
β-Iodoallenolate Cyclization with Alkynone **2**.



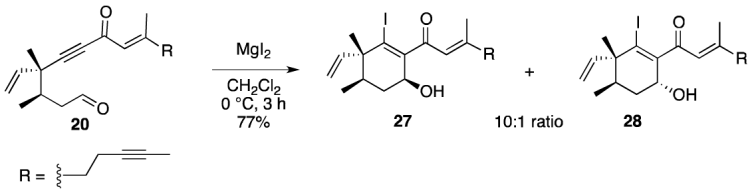
Scheme 5.
Synthesis of Oxadecalin **1** using BF_3COEt_2 as Promoter



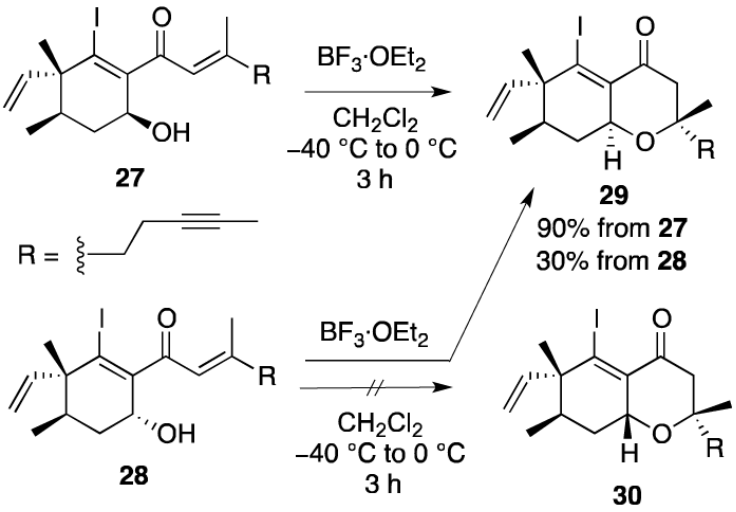
Scheme 6.
Diastereoselectivity in the Intramolecular Aldol Reaction.



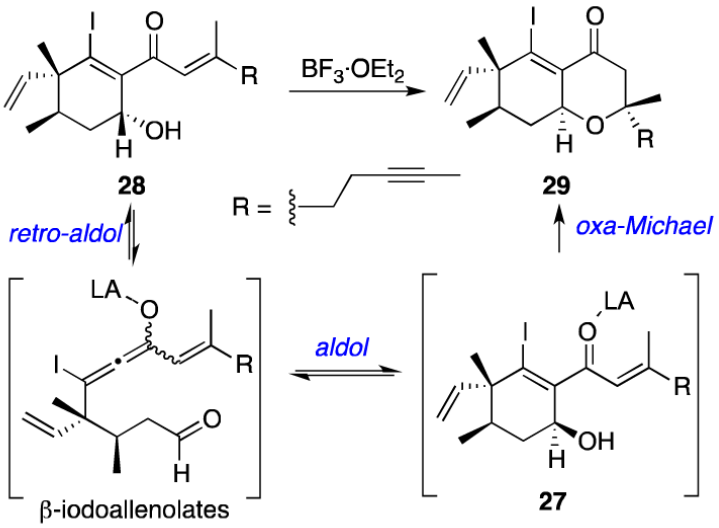
Scheme 7.
Synthesis of Alkynone **20**



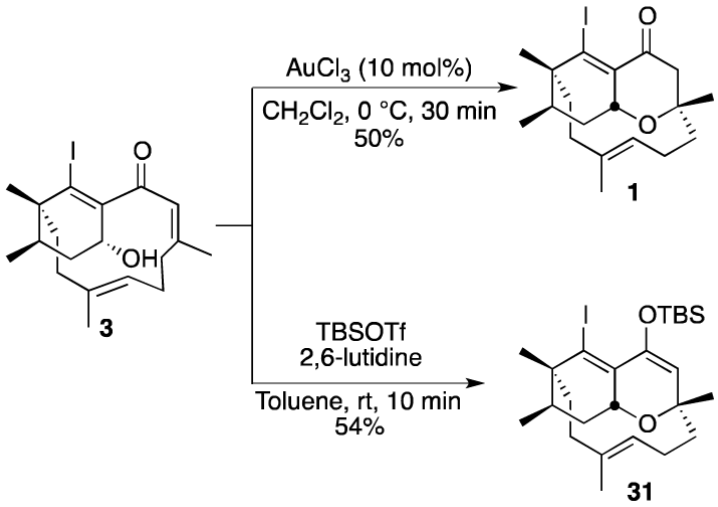
Scheme 8.
Intramolecular Aldol Reaction of Alkynone **20**.



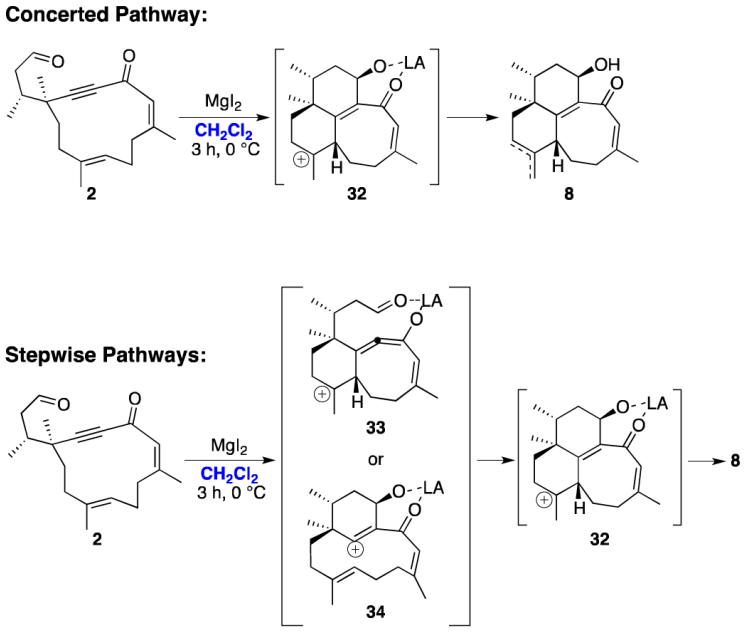
Scheme 9.
Oxa-Michael Reactions of **27** and **28**



Scheme 10.
Cyclization of **28** via Retro-Aldol Reaction Pathway



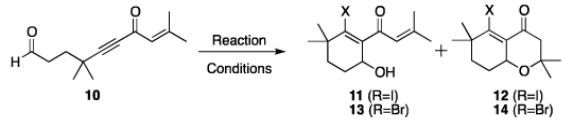
Scheme 11.
Alternative Methods for Inducing Oxa-Michael Cyclization in Cyclohexenyl Alcohol **3**.



Scheme 12.
Proposed Mechanisms for the Formation of Tricycles **8**.

Table 1

β-Haloallenolate Cyclizations.[a]



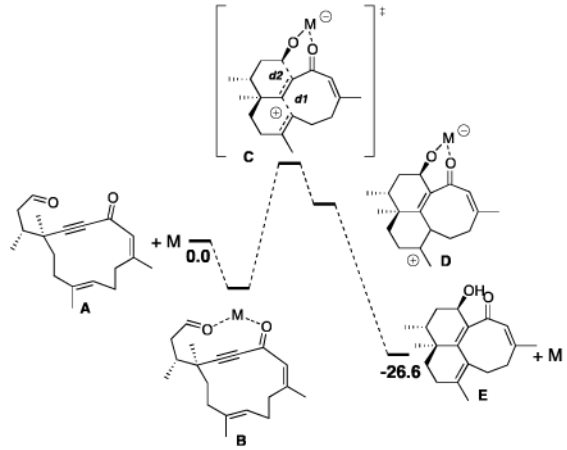
Entry	Lewis Acid	Iodide	Conditions	product	Yield
1	$TiCl_4$	*n*-Bu_4NI	−78 °C to 0 °C, 2 h	**11**	82%
2	MgI_2	---	0 °C, 3 h	**11**	75%
3	$BF_3{\cdot}OEt_2$	*n*-Bu_4NI	−40 °C to 0 °C, 3 h	**12**	77%
4	$MgBr_2$	---	0 °C to rt, 24 h	**13**	52%[b]
5	$BF_3{\cdot}OEt_2$	*n*-Bu_4NBr	−40 °C to rt, 7 h	**14**	46%

[a]*Reaction conditions*: Alkynone (1.0 equiv), Lewis acid (1.3 equiv), and *n*-Bu_4NX (1.3 equiv) in CH_2Cl_2 (0.10 M) for the indicated time at the indicated temperature.

[b]65% conversion.

Table 2

Computed Intermediates and Gibbs Free Energies After Solvation Correction (B3LYP/6-311G**[Mg,I]/6-31G*[other elements]//PCM; kcal/mol) Corresponding to the Formation of the Tricyclic Framework.



Entry	M	ΔG_{AB}		$[\Delta G_{AC}]^{\ddagger}$		ΔG_{AD}		*d1* (Å)	*d2* (Å)
		DCM	THF	DCM	THF	DCM	THF		
1	MgI_2	−1.3	−2.8	25.0	24.2	18.2	17.6	1.68	1.95
2	$MgI_2 \cdot 2THF$	–	10.0	–	39.2	–	3.0	1.68	1.97
3	MgI^+	−1.3	−1.3	26.8	25.0	26.0	23.6	1.85	2.64
4	$MgI^+ \cdot THF$	–	−15.3	–	8.9	–	0.2	1.66	2.12
5	Mg^{2+}	−0.5	−4.6	16.1	12.0	5.3	1.2	1.61	2.30