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High π-Facial and *exo*-Selectivity for the Intramolecular Diels–Alder Cycloaddition of Dodeca-3,9,11-trien-5-one Precursors to 2-*epi*-Symbioimine and Related Compounds

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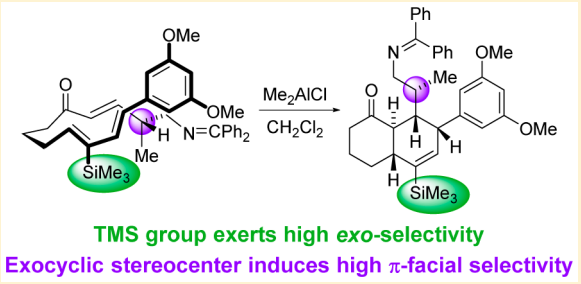
Supporting Information

ABSTRACT: An unconstrained exocyclic stereogenic center and a removable trimethylsilyl group are combined to induce high π-facial selectivity and near-exclusive *exo*-selectivity in the intramolecular Diels–Alder cycloaddition of dodeca-3,9,11-trien-5-ones. This strategy provides direct access to polysubstituted *trans*-1-decalones related to the symbioimines in good yield and acceptable diastereoselectivity.

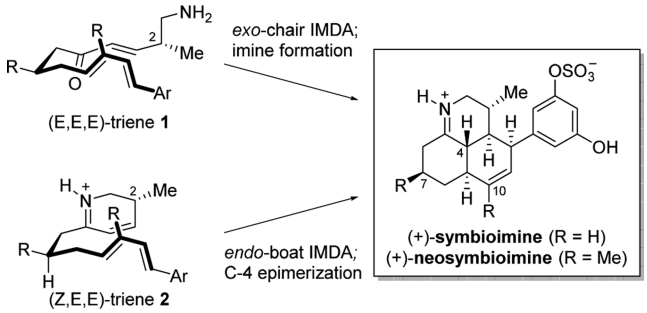


INTRODUCTION

The intramolecular Diels–Alder (IMDA) cycloaddition is a powerful and atom-economical tool for the stereoselective construction of complex polycyclic natural products and natural product-like frameworks.[1] In spite of intense worldwide investigations, there still remains unconquered territories in the IMDA methodological domain. We have used the originally proposed biosynthesis of the tricyclic framework present in the symbioimine family of iminium alkaloids as an inspiration to explore some of these remaining holes in the IMDA tactic.[2] Herein, we report on the use of a trimethylsilyl group as a removable stereocontrol element to affect the highly *exo*-selective type I IMDA cyclization of dodeca-3,9,11-trien-5-ones. Additionally, we provide further support to our previous observations that a single unconstrained exocyclic stereogenic center is sufficient to effectively control the π-facial selectivity in these cycloadditions.[2a] Combining these two stereocontrol elements provides uniquely direct and stereoselective access to substituted *trans*-1-decalones.

Uemura and co-workers isolated (+)-symbioimine[3] and (+)-neosymbioimine[4] from a symbiotic dinoflagellate *Symbiodinium* sp. colonizing a marine flatworm *Amphiscolops* sp. While no biological activity has been reported for its 7,10-dimethylated congener, (+)-symbioimine is known to exhibit moderately selective COX-2 inhibition and promising anti-osteoclastogenic activity. As proposed by the original isolators, the tricyclic iminium core of the symbioimines could arise from either a cascade involving an *exo*-chair IMDA cycloadditon of (*E*)-enone **1** and imine cyclization or an *endo*-selective IMDA reaction of dihydropyridinium **2** followed by epimerization at C-4 (Scheme 1). Snider[5] and Thomson[6] both employed the dihydropyridinium route in their respective syntheses of

Scheme 1. Proposed Biosyntheses of the Symbioimines



symbioimine. These groups noted, however, that the dihydropyridinium intermediate is prone to disproportionation and other side reactions, thus severely restricting the yield of the key IMDA cycloaddition.[8] The other proposed biosynthetic route to the tricyclic core is essentially unprecedented on at least two fronts. First, the π-facial selectivity for the IMDA reaction toward (+)-symbioimine (R = H) must be controlled exclusively by a single unconstrained exocyclic stereocenter. While there are several examples of rotationally restricted exocyclic chirality centers successfully governing the π-facial selectivity for related trienone IMDA substrates,[5−7] previous attempts with only freely rotating exocyclic stereocenters, such as that found in **1**, typically fail to elicit appreciable diastereoselectivity in type I IMDA cycloadditions.[7a] More importantly, when *all-trans* trienones such as **1** (R = H) undergo type I IMDA cycloadditions, they typically proceed via

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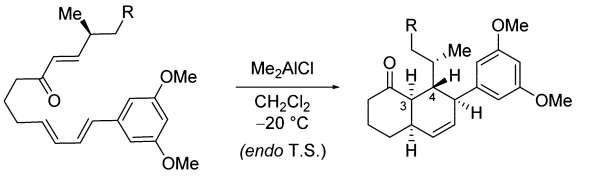
an *endo* transition state instead of the requisite *exo*-chair pathway.[1a,9] Yamamoto demonstrated that bulky aluminum phenoxide Lewis acids can encourage *exo*-selective IMDA reactions of related (*E*,*E*,*E*)-trienones.[10] This strategy is limited, however, to substrates possessing relatively electron-rich diene components. Unfortunately, the 3,5-dihydroxybenzene substituent in **1** (depicted as "Ar" in Scheme 1) deactivates the diene fragment while providing opportunities for competing intramolecular Friedel–Crafts-type reactions with the ketone moiety under Lewis acidic conditions.[5,11] In short, methods for the conversion of relatively deactivated (*E*,*E*,*E*)-trienones such as **1** into the corresponding *trans*-deca-6-en-1-ones via an *exo* transition state and with high π-facial selectivity are currently absent in the rich IMDA repertoire.

RESULTS AND DISCUSSION

Our initial attempts to address these limitations involved the Lewis acid-mediated type I IMDA reaction of (*E*,*E*,*E*)-trienones **3a–c** (Scheme 2).[2a] As expected, the cycloadditions all

Scheme 2. Previous Studies[2a]



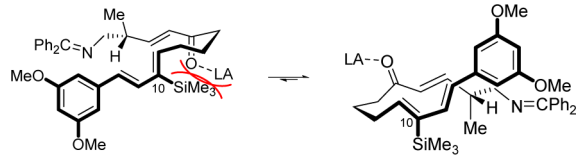
(±)-**3a** (R = NHBoc)
(+)-**3b** (R = OPiv)
(+)-**3c** (R = OTBDPS)

(±)-**4a** (R = NHBoc, 88%, dr >20:1)
(+)-**4b** (R = OPiv, 52%, *dr* 4.5:1)
(+)-**4c** (R = OTBDPS, 76%, *dr* 3:1)

proceeded via an *endo* transition state. Dimethylaluminum chloride proved to be the best Lewis acid mediator. Use of Yamamoto's relatively less Lewis acidic bulky aluminum phenoxide reagents[10] in hopes of favoring the *exo* product failed to afford any conversion of *N*-Boc-protected **3a**. Surprisingly, the *endo*-selective cycloaddition of **3a** afforded essentially one single diastereomer **4a**, indicating that it is possible for a single unconstrained exocyclic stereogenic center to dictate the π-facial selectivity for a type I IMDA reaction of 1,7,9-decatrien-3-ones. This remarkable π-facial selectivity was highly dependent on the nature of the R group born in trienones **3**. While Boc-protected amine **3a** cyclized to essentially a single diastereomer, the corresponding protected alcohols **3b** and **3c** demonstrated markedly lower diastereoselectivities (*dr* 4.5:1 for **4b** and 3:1 for **4c**). In all cases, the major diastereomer is doubly epimeric to (+)-symbioimine at C-3 and C-4. All attempts to affect a similar *endo*-selective IMDA cycloaddition of the corresponding (*Z*)-enones, so as to obtain the symbioimine stereochemistry, resulted in complete isomerization back to (*E*)-enones **3** prior to any IMDA cycloaddition.

While our previous studies were the first to successfully address the π-facial selectivity issue, the matter of promoting the *exo* transition state remained elusive. To overcome this hurdle, we were inspired by reports first from Boeckman and later from Roush in which they both employed a trimethylsilyl (TMS) moiety as a removable stereodirecting group to alter the diastereoselectivity for the *endo*-selective IMDA cyclization of *externally* activated undeca-2,8,10-trienoates.[12] While this tactic had yet to be used for inducing an *exo*-selective IMDA process, we hypothesized that incorporating a TMS group onto C-10 (symbioimine numbering) of our *internally* activated trienone IMDA precursor should destabilize the *endo* transition states via steric interactions with the carbonyl-Lewis acid complex (Scheme 3).[13,18] Additionally, the C-10 TMS group should

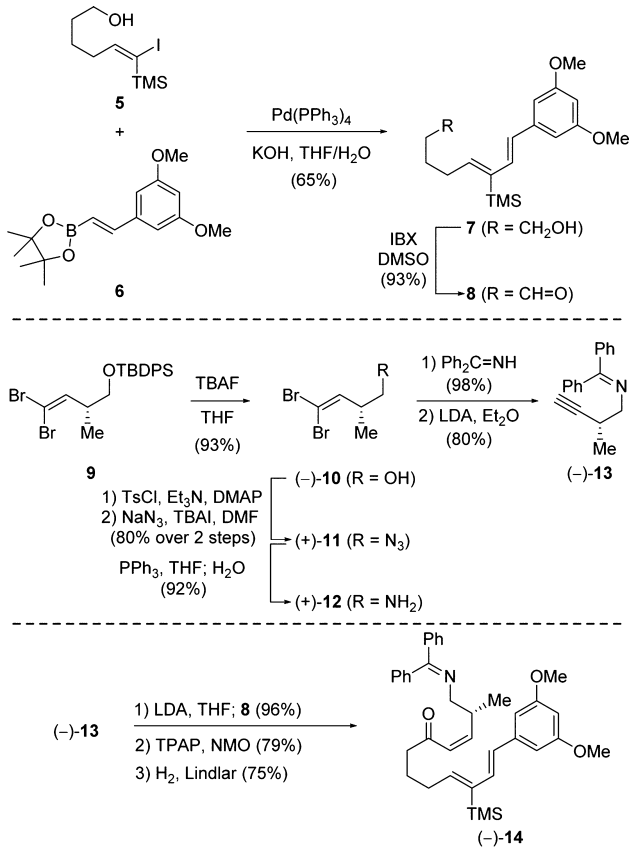
Scheme 3. Two Potential Transition State Conformations[18]



encourage the diene fragment to adopt the necessary *s-cis* conformation.[14] Finally, we chose to maximize the stereodirecting effect of the exocyclic chirality center without sacrificing the ease of endgame manipulations by switching the Boc group present in **3** to a larger benzophenone imine moiety.

Synthesis of the requisite trienone IMDA precursor **14** involved the modular coupling of three key fragments (Scheme 4). First, Suzuki–Miyaura cross coupling of vinyl iodide **5**

Scheme 4. Synthesis of IMDA Precursor (−)-14



(available in two steps from hex-5-yn-1-ol)[15] and commercially available boronate ester **6** afforded dienol **7** in a usable isolated yield.[16] Oxidation to the corresponding aldehyde **8** with IBX proceeded smoothly. The other necessary fragment, chiral iminoalkyne **13**, was obtained in six steps and 54% overall yield from **9** (available in three steps from (*S*)-(+)-Roche ester).[2a] Finally, coupling between the lithium alkynide of **13** and aldehyde **8**, followed by oxidation of the resultant alcohol, and partial hydrogenation of the triple bond afforded the desired

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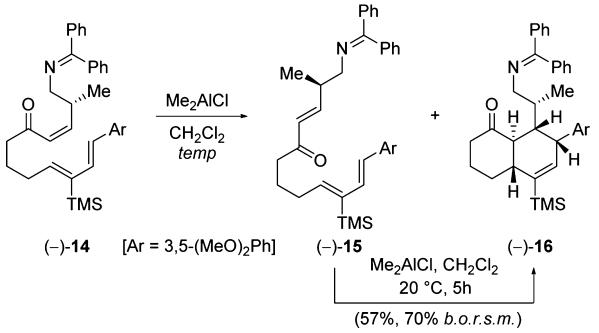
(*Z*)-enone **14** in 57% isolated yield over the three steps. Based on our previous studies,[2a] it was presumed that *Z*-to-*E* enone isomerization would precede IMDA cycloaddition, so (*Z*)-enone **14** was viewed as a viable precursor to the corresponding (*E*)-enone **15**.

With trienone **14** in hand, we explored its Lewis acid-mediated IMDA cyclization at various temperatures (Table 1).

Table 1. IMDA Cyclization of Trienone (−)-14[a]



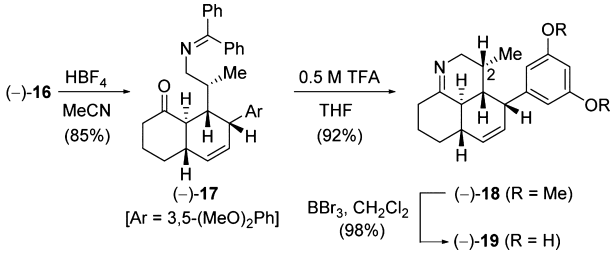
			Yield[b] (%)	
entry	temp (°C)	time (h)	(−)-**15**	(−)-**16** (*exo*:*endo*)[c]
1	−78	24	36[d]	0 (n.d.)
2[e]	−78 → −30	12	14	43 (≥20:1)
3	−20	4	4	42 (14:1)
4	20 (rt)	5	4	64 (12:1)

[a]Reaction conditions: Me_2AlCl (1.2 equiv) in CH_2Cl_2 (0.03 M). [b]Isolated yield after column chromatography for a single run. [c]Determined by ^1H NMR analysis of the crude reaction product. [d]Starting (Z)-enone **14** recovered in 22%. [e]1.5 equiv of Me_2AlCl used.

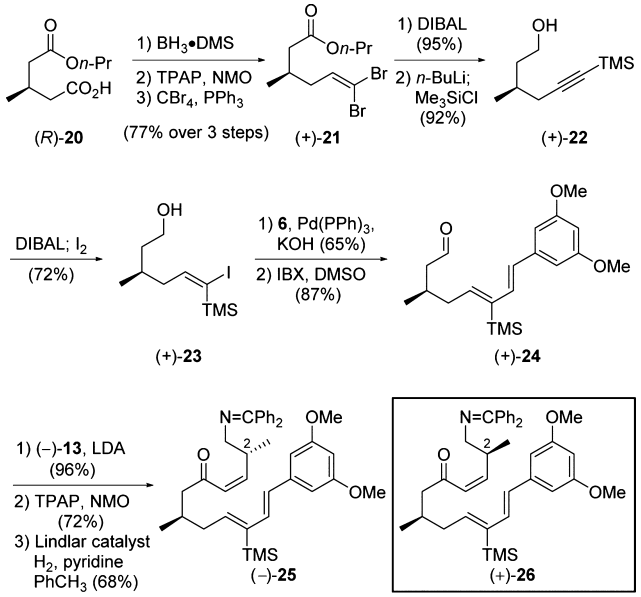
Similar to our previous studies,[2a] only partial enone isomerization (**14** → **15**) was observed at −78 °C (entry 1). Letting the reaction warm up to −30 °C over 12 h led to the formation of a single IMDA product **16** in 43% isolated yield along with 14% of (*E*)-enone **15** (entry 2). The relative stereochemistry within the *trans*-1-decalone unit of **16** was readily deduced by standard 2D-NMR techniques (Table S1 in the Supporting Information).[17] Determination of the absolute stereochemistry required conversion to the tricyclic imine **19** and comparison to known compounds.[3,6] This was accomplished in high overall yield by selective removal of the vinyl TMS group with borofluoric acid, followed by transimination with trifluoroacetic acid and BBr_3-mediated cleavage of the phenolic methyl ethers (Scheme 5). The resulting product **19** is pseudoenantiomeric to (+)-symbioimine; only the initial chirality center at C-2 matches the natural product configuration. This is most evident in the ^1H NMR analysis of **19**. The protons on the C-2 methyl group are shifted upfield significantly in **19** versus (+)-symbioimine (δ 0.13 vs 1.05 ppm, respectively), indicating that this moiety is directly across from the π-face of the aromatic ring. As designed, the TMS group in trienone **14** directs the IMDA reaction to proceed preferentially via an *exo* transition state (Scheme 3).[18] The exquisite π-facial selectivity induced by the C-2 chirality center is identical to that seen in the *endo*-selective IMDA cycloaddition of (*E*)-enone **3a** (Scheme 2).[2a] Performing the IMDA reaction at −20 °C gave a similar isolated yield of cycloaddition products with a slight reduction in the diastereomeric ratio (Table 1, entry 3). The best isolated yields with an acceptable *exo*:*endo* ratio were obtained by performing the reaction at ambient temperature (entry 4). The minor *endo* product was never isolated in sufficient quantity or purity to allow for proper determination of its absolute stereochemistry. When (*E*)-enone **15** was subjected to the reaction conditions, results identical to those observed with (*Z*)-enone **14** were obtained, corroborating our assumption that enone isomerization most likely precedes IMDA cycloaddition.

To investigate the influence of a stereocenter in the connecting chain on the diastereoselectivity of the *exo*-selective IMDA reaction, we synthesized trienone **25** from known propyl ester **20** (available via the enzymatic desymmetrization of 3-methylglutaric anhydride)[19] following a strategy similar to that used for **14** (Scheme 6). The carboxylic acid moiety in **20** was

Scheme 5. Synthesis of Tricyclic Imine (−)-19



Scheme 6. Synthesis of IMDA Precursors 25 and 26



selectively converted into the corresponding *gem*-dibromoalkene **21** in three steps and 77% yield. Reduction of the ester and conversion to the corresponding TMS-alkyne **22** proceeded smoothly. *Syn*-selective hydroiodination of alkyne **22** afforded vinyl iodide **23** in 72%.[15] Suzuki−Miyaura cross coupling between iodide **23** and boronate ester **6**, followed by oxidation of the primary alcohol, afforded dienal **24** in 57% over the two steps. Coupling between the resultant aldehyde **24** and the lithium alkynide of (−)-**13**, followed by oxidation and partial hydrogenation, as before, completed the synthesis of (−)-**25** in 47% over the three steps. The C-2 epimer (+)-**26** was obtained following an identical procedure employing the lithium alkynide of (+)-**13**, which was available from the (*R*)-(−)-Roche ester.

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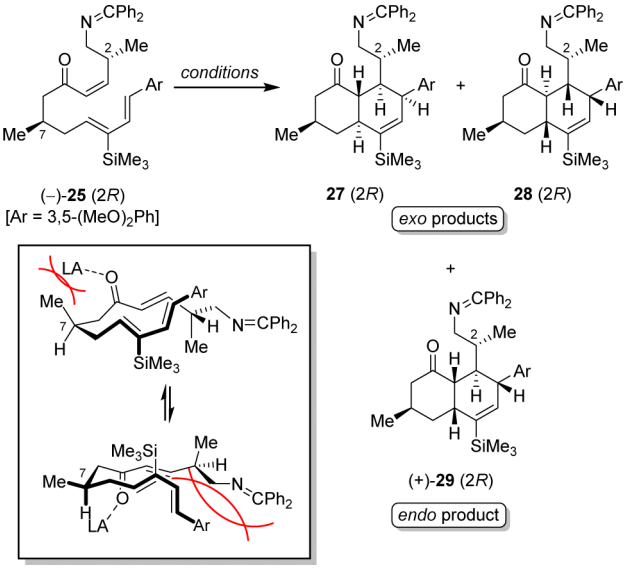
Table 2. IMDA Cycloaddition of Trienone (−)-25

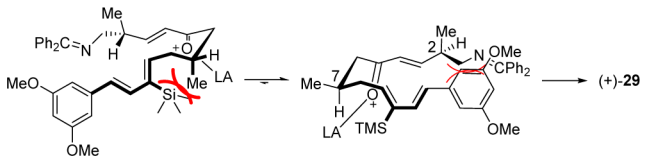


entry	conditions	27:28:29[a]	Yield (%)
1	Me_2AlCl (1.5 equiv), CH_2Cl_2, −20 °C, 5 h	1:2.4:2.7	85[b]
2	$BF_3{\cdot}Et_2O$ (1.5 equiv), CH_2Cl_2, −10 °C, 3.5 h	2:1:0.3	61[c]

[a]Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [b]Combined isolated yields of **27**−**29** after column chromatography for a single run. [c]Combined isolated yield of exo products **27** and **28** only.

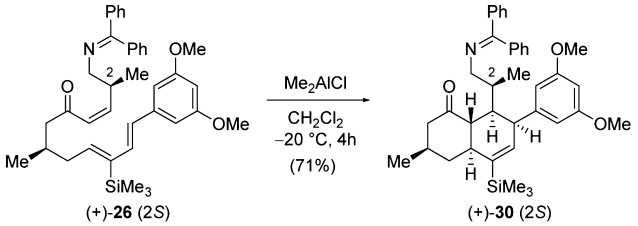
When **25** was treated with Me_2AlCl at −20 °C, one *endo* (**29**) and two *exo*-IMDA products (**27** and **28**) were isolated in 85% combined yield as a 2.7:1:2.4 ratio of diasasteromers, respectively (Table 2, entry 1). When $BF_3{\cdot}Et_2O$ was used as the Lewis acid, the *exo*:*endo* ratio increased dramatically and there was a switch in diastereoselectivity now favoring *exo*-product **27** (entry 2).[26] Based on our previous observations that *Z*-to-*E* enone isomerization seems to precede cycloaddition, it is assumed that all three cycloaddition products arise from the corresponding (*E*)-enone of **25**. The sole *endo* product **29** is most likely the result of a chair transition state bearing an equatorial C-7 methyl group, but π-facial selectivity counter to the C-2 stereogenic center (Scheme 7). The relatively low

Scheme 7. Transition State Conformation for Formation of *endo* Product (+)-29



selectivity between the two *exo* products **27** and **28** indicates that there is a stereocontrol mismatch between the exocyclic C-2 chirality center and the endocyclic C-7 methyl group. If the connecting chain adopts a chair conformation in the transition state,[18] our previous results suggest that the π-facial selectivity induced by the C-2 stereocenter would require the C-7 methyl group to reside in an axial position, leading to **28** (Table 2, inset top). The other diastereomer **27** could arise from an alternate chair conformation with opposite π-facial approach but an equatorial C-7 methyl group. To further explore the relationship between these two stereocontrol elements, we submitted trienone (+)-**26**, which is the C-2 epimer of (−)-**25**, to the IMDA reaction conditions (Scheme 8). In this "matched" case, only one IMDA product (**30**) was observed and isolated in 71% yield.

Scheme 8. IMDA Cycloaddition of (+)-26



Inspired by the revelation that the C-10 TMS *exo*-IMDA product **27** contains the same absolute stereochemistry as (+)-neosymbioimine, we attempted to directly access this natural product architecture via the Lewis acid-mediated IMDA cycloaddition of C-10 methylated trienone **34**. Synthesis of the requisite trienone **34** began with Suzuki−Miyaura cross coupling between *gem*-dibromoalkene **21** and boronate ester **6** to afford bromodiene **31** (Scheme 9). The best yield (71%) for this cross coupling reaction was obtained when Tl_2CO_3 was used as a base. After considerable experimentation, alternate reaction conditions that avoided the use of superstoichiometric amounts of toxic thallium salts but still afforded acceptable isolated yields of the diene **31** were eventually discovered. Namely, the combination of $Pd_2(dba)_3$ (3 mol %) and tri-2-furylphosphine (TFP, 16 mol %) as catalyst and cesium carbonate as base in a 4:1 mixture of dioxane and water generated diene **31** in 66% yield at gram scale. Palladium-catalyzed Negishi cross coupling between bromodiene **31** and dimethylzinc followed by $LiAlH_4$-mediated reduction of the ester moiety afforded alcohol **32** in 93% yield over the two steps. Oxidation of the primary alcohol with IBX in DMSO

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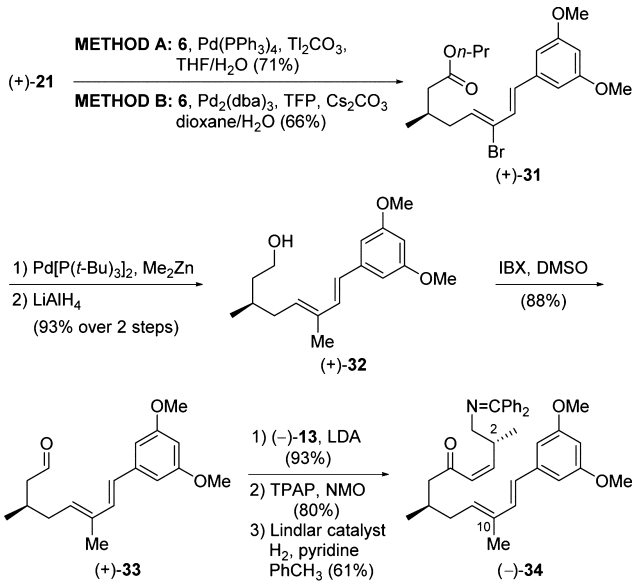
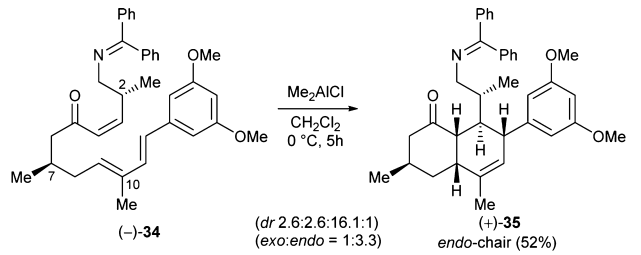
Scheme 9. Synthesis of C-10 Methylated Trienone (−)-34



afforded aldehyde **33**, which was then converted to the desired (*Z*)-trienone **34** in three steps and 45% overall yield following procedures identical to those used to obtained enones **14** and **25**.

In contrast to our observations with the Lewis acid-mediated IMDA of TMS-trienones **14**/**15** (Table 1), **25** (Table 2), and **26** (Scheme 8), treatment of C-10 methylated **34** with Me_2AlCl provided a complex mixture of all four possible diastereomers, from which only the highly predominant *endo* product **35** could be isolated cleanly and in moderate yield (Scheme 10).

Scheme 10. IMDA Cycloaddition of (−)-34



Apparently, the C-10 methyl group in **34** is not large enough to induce a preference for the *exo* transition states like the bulkier TMS group in related trienones **25** and **26**.[27] As with the formation of *endo* adduct **29**, the major product **35** could arise via an *endo*-chair transition state in which the C-7 methyl group overwhelms the influence of the C-2 stereocenter (*c.f.* Scheme 7). Attempting the Lewis acid-mediated IMDA reaction at a lower temperature (−15 °C) only resulted in isomerization to the corresponding (*E*)-enone without any cycloaddition.

In summary, we have demonstrated that the combination of a bulky TMS substituent on the diene fragment and a single unconstrained exocyclic chirality center is sufficient to induce high *exo* selectivity and diastereoselectivity in the Lewis acid-mediated IMDA cycloaddition of internally activated dodeca-3,9,11-trien-5-ones. Chirality centers in the connecting chain complicate the diastereoselectivity without canceling the high *exo*-selectivity. As an additional benefit, our studies highlight the remarkable utility of the benzophenone imine as a protection for primary amines.[20] We demonstrated that this moiety can survive Lindlar catalytic hydrogenation, both strongly basic and Lewis acidic conditions, various oxidants, and even aqueous borofluoric acid, yet it can be removed readily with 0.5 M TFA in THF. Overall, our efforts provide direct access to previously unavailable epimers of the symbioimine tricyclic imine framework requisite for ongoing structure−activity relationship studies

EXPERIMENTAL SECTION

General Methods. All nonaqueous reactions were performed in oven-dried flasks or vials under an atmosphere of dried and deoxygenated argon with dry solvents and magnetic stirring, unless stated otherwise. All solvents were dried by storing over activate 3 Å molecular sieves for at least 48h and sparged with dried and deoxygenated argon gas for at least 30 min.[21] Chiral vinyl dibromide **9** was obtained as a single enantiomer (≥98% *ee*) in three steps from (*S*)-(+)-Roche ester following previously described methods.[2a,22] The enantiomer of **9**, required for the synthesis of (+)-**13** and (+)-**26** was obtained from (*R*)-(−)-Roche ester following identical procedures. Commercially available boronate ester **6** was also obtained in large scale from the hydroboration of the corresponding alkyne using pinacol borane and Schwartz's catalyst ($HZrCp_2Cl$). Dienes (+)-**31** and (+)-**32** were previously reported by our group.[25] All other reagents were purchased from commercial sources and used as received. All chromatography was performed with indicated solvents and 60 Å 230−400 mesh silica gel. Unless otherwise noted, all yields in the main text refer to average isolated yields after column chromatography of at least three separate runs at different scales. Accordingly, these yields may differ from the specific examples provided below. Melting points are uncorrected. Infrared spectra were obtained using a thin film deposited on freshly made KBr disks; only strong and functional group-specific peaks are reported (in cm^{-1}). Optical rotation was determined on a 10 cm length polarimeter cell; all $[\alpha]_D$ values are given in 10^{-1} $degcm^2g^{-1}$ at 20 °C. All NMR spectra were taken on a 400 or 500 MHz spectrometer at 300 K, as indicated. Chemical shifts are reported in δ (ppm) units using residual solvent peak as a standard.[23] Initial diastereomeric ratios determined from ^1H NMR analysis of the crude reaction mixtures. High resolution mass spectra obtained using an LCMS-IT-TOF.

(5Z,7E)-8-(3,5-Dimethoxyphenyl)-6-(trimethylsilyl)octa-5,7-dien-1-ol (7). Vinyl iodide **5** (1.56 g, 5.23 mmol)[15] and boronate ester **6** (1.97 g, 6.79 mmol, 1.3 equiv) were dissolved in a mixture of THF (18 mL) and deionized H_2O (6 mL). Argon was bubbled through the solution for 30 min, then KOH (0.4 g, 7.13 mmol, 1.36 equiv) and $Pd(PPh_3)_4$ (900 mg, 0.78 mmol, 15 mol %) were added. The resulting mixture was stirred at rt for 1 h and then 50 °C for 3 h. After cooling to rt, the reaction was diluted with 50 mL EtOAc, then washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography (20% EtOAc/hexane) to give diene **7** (1.16 g, 3.47 mmol, 66%) as a pale brown oil: R_f = 0.33 (20% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 15.8, 0.9 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 2H), 6.37 (dd, *J* = 10.9, 7.6 Hz, 1H), 6.35−6.31 (m, 2H), 3.80 (s, 6H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.27 (q, *J* = 7.5 Hz, 2H), 1.68−1.59 (m, 2H), 1.56−1.48 (m, 2H), 1.33 (s, 1H), 0.25−0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 145.1, 140.4, 138.5, 135.5, 127.1, 104.1, 99.2, 62.8, 55.2, 32.2, 31.9, 26.2, 0.9; IR (thin film) ν 3440, 2394, 1590, 1153; HRMS (E+) *m*/*z* 357.1851 $(M+Na)^+$; calculated mass for $C_{19}H_{30}NaO_3Si^+$: 357.1856.

(5Z,7E)-8-(3,5-Dimethoxyphenyl)-6-(trimethylsilyl)octa-5,7-dienal (8). To a solution of alcohol **7** (1.15 g, 3.44 mmol) in 12 mL DMSO at rt was added IBX (1.44 g, 5.15 mmol, 1.5 equiv) and the solution was stirred at rt for 4 h. The resulting mixture was then diluted with saturated aq $NaHCO_3$ and extracted with Et_2O. The combined organic extract was washed with 5% aq LiCl, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography (20% Et_2O/hexane) to afford diene **8** (1.06 g, 3.19 mmol, 93%) as a pale yellow oil: R_f = 0.38 (20% Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.5 Hz, 1H), 6.77 (d, *J* = 16.1 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 2H), 6.38 (d, *J*

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= 15.8 Hz, 1H), 6.34 (t, J = 2.2 Hz, 1H), 6.28 (td, J = 7.5, 1.0 Hz, 1H), 3.80 (s, 6H), 2.50 (tt, J = 7.3, 3.5 Hz, 2H), 2.28 (dd, J = 14.9, 7.5 Hz, 2H), 1.78 (p, J = 7.4 Hz, 2H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 161.0, 143.6, 140.2, 139.9, 135.2, 127.7, 104.4, 99.4, 55.5, 43.5, 31.3, 22.4, 0.7; IR (thin film) ν 2953, 2837, 2720, 1725, 1590; HRMS (E+) m/z 355.1691 $(M+Na)^+$; calculated mass for $C_{19}H_{28}NaO_3Si^+$: 355.1700.

*(R)-4,4-Dibromo-2-methylbut-3-en-1-ol [(−)-**10**].* To a stirred solution of **9** (14.8 g, 30.7 mmol)[2a,22] and 160 mL THF in a Nalgene screw-top plastic bottle at 0 °C was added dropwise tetrabutylammonium fluoride (1.0 M in THF, 46.0 mL, 46.0 mmol, 1.5 equiv) and the resulting mixture was stirred at 0 °C for 4 h. The reaction was then quenched with 150 mL saturated aq $NaHCO_3$, extracted with Et_2O (4 × 150 mL), dried ($MgSO_4$), and purified by flash chromatography (20% Et_2O/hexane) to provide alcohol (−)-**10** (7.05 g, 28.9 mmol, 94%) as a colorless oil. The resulting product was spectroscopically identical to the known enantiomer.[23,24] **NOTE**: Prolonged reaction times, higher temperature, and more TBAF all resulted in the competitive elimination of HBr to form the corresponding bromoalkyne. R_f = 0.32 (20% Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 9.3 Hz, 1H), 3.66−3.45 (m, 2H), 2.85−2.61 (m, 1H), 1.59 (s, 1H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 89.7, 66.3, 41.2, 15.5; $[\alpha]_D$ = −0.45 (c 0.67, $CHCl_3$).

*(R)-4-Azido-1,1-dibromo-3-methylbut-1-ene [(+)-**11**].* To a stirred solution of (−)-**10** (3.4 g, 13.9 mmol), Et_3N (10 mL, 71.7 mmol, 5.2 equiv), and DMAP (86 mg, 0.8 mmol, 5 mol %) in 20 mL CH_2Cl_2 at 0 °C was added dropwise via addition funnel a solution of p-TsCl (4.03 g, 21.14 mmol, 1.5 equiv) in 30 mL CH_2Cl_2. The reaction then was allowed to warm up to 25 °C and stirred at that temperature overnight. The resulting reaction mixture was diluted with Et_2O (100 mL), washed sequentially with saturated aq $NaHCO_3$ (2 × 50 mL), H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), concentrated *in vacuo*, and carried on directly to the next step without further purification.

To a stirred solution of the resulting p-toluenesulfonate ester in 40 mL DMF at ambient temperature was added tetrabutylammonium iodide (259 mg, 0.7 mmol, 5 mol %) and sodium azide (3.66 g, 56.3 mmol, 4 equiv). The resulting mixture was heated to 50 °C and stirred at that temperature overnight. After cooling back to rt, the reaction was diluted with 150 mL Et_2O, washed sequentially with H_2O (3 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and purified by flash chromatography (hexanes) to provide azide (+)-**11** (2.83 g, 10.5 mmol, 76%) as a colorless oil: R_f = 0.51 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, J = 9.2 Hz, 1H), 3.27 (d, J = 6.4 Hz, 2H), 2.85−2.68 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 90.5, 55.6, 38.7, 16.8; IR (thin film) ν 2971, 2929, 2870, 2099, 1616, 1454, 1257; $[\alpha]_D$ = +1.25 (c 0.56, CH_2Cl_2); HRMS (E+) m/z 243.9126 $(M+3H-N_2)^+$; calculated mass for $C_5H_{10}Br_2N^+$: 243.9154. **NOTE:** The azide decomposes to the corresponding amine under HRMS conditions.

*(R)-4,4-Dibromo-2-methylbut-3-en-1-amine [(+)-**12**].* To a solution of azide (+)-**11** (5.9 g, 21.94 mmol) in 70 mL dry THF at rt was added in one portion PPh_3 (23 g, 87.75 mmol, 4 equiv). The resulting solution was heated to 50 °C and stirred for 3 d. H_2O (5 mL) was then added and the resulting mixture was stirred at 50 °C for an additional 5 h. The resulting reaction mixture was concentrated *in vacuo* and immediately purified by flash chromatography (5% MeOH/CH_2Cl_2) to provide amine (+)-**12** (4.9 g, 20.8 mmol, 92%) as a brown oil: R_f = 0.28 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (d, J = 9.3 Hz, 1H), 2.73−2.58 (m, 2H), 2.57−2.45 (m, 1H), 1.30 (s, 2H), 1.01 (dd, J = 6.7, 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 89.1, 47.4, 42.2, 16.7; IR (thin film) ν 3376, 3290, 2963, 2926, 2666, 1611, 1456;:$[\alpha]_D$ = +7 (c 0.5, CH_2Cl_2); HRMS (E+) m/z 243.9122 $(M+H)^+$; calculated mass for $C_5H_{10}Br_2N^+$: 243.9154.

*(R)-N-(Diphenylmethylene)-2-methylbut-3-yn-1-amine [(−)-**13**].* Amine (+)-**12** (4.72 g, 19.43 mmol) was dissolved in dry CH_2Cl_2 and conc HCl was added dropwise to the stirred mixture until no additional solid formed. The solvent was removed *in vacuo* and the resulting solid was dried further under vacuum in the presence of P_2O_5 for 2 d. The resulting ammonium chloride salt was slurried in 35 mL CH_2Cl_2 and benzophenone imine (4 mL, 23.84 mmol, 1.2 equiv) was added via syringe.[20] The reaction mixture was stirred at rt for 2 d, filtered, and concentrated *in vacuo*. Purification of the resulting residue by flash chromatography (1% Et_3N in 2% EtOAc/hexane) afforded the corresponding benzophenone imine (7.75 g, 19.03 mmol, 98%) as a pale yellow oil: R_f = 0.54 (5% EtOAc/hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.83 (dt, J_o = 8.0 Hz, J_m = 3.0 Hz, 2H), 7.14−7.00 (m, 6H), 6.90−6.81 (m, 2H), 6.29 (d, J = 9.3 Hz, 1H), 3.25−3.13 (m, 2H), 2.97−2.82 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 168.5, 143.1, 140.2, 137.4, 132.1, 130.2, 128.9, 128.8, 128.2, 128.0, 88.6, 58.0, 40.4, 17.1; IR (thin film) ν 3059, 2964, 2925, 1661, 1623, 1446, 1278; $[\alpha]_D$ = −39 (c 0.28, CH_2Cl_2); HRMS (E+) m/z 407.9766 $(M+H)^+$; calculated mass for $C_{18}H_{18}Br_2N^+$: 407.9781.

To a solution of the resulting dibromoalkene (1.9 g, 4.67 mmol) in 30 mL Et_2O at −78 °C was added LDA (2 M solution in THF, 7 mL, 3 equiv). The resulting mixture was stirred at −78 °C for 8h, then warmed to rt and quenched with solid NH_4Cl. **NOTE**: TLC never showed completion. The resulting mixture was filtered, concentrated *in vacuo*, and immediately purified by flash chromatography (1% Et_3N in 2% EtOAc/hexane) to provide the starting material (15% recovery) and alkyne (−)-**13** (925 mg, 3.73 mmol, 80%, 94% *borsm*) as a yellow oil: R_f = 0.48 (5% EtOAc/hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.92−7.84 (m, 2H), 7.14−6.99 (m, 6H), 6.93−6.87 (m, 2H), 3.56 (dd, J_{AB} = 13.7 Hz, J_{AX} = 6.0 Hz, 1H), 3.37 (dd, J_{BA} = 13.7 Hz, J_{BX} = 7.4 Hz, 1H), 3.04−2.91 (m, 1H), 1.84 (d, J = 2.4 Hz, 1H), 1.24 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 168.4, 140.3, 137.3, 132.1, 130.2, 129.0, 128.7, 128.2, 127.9, 87.9, 69.4, 59.4, 28.4, 19.1; IR (thin film) ν 3299, 2925, 1625, 1446; $[\alpha]_D$ = −10.5 (c 0.38, CH_2Cl_2); HRMS (E+) m/z 248.1426 $(M+H)^+$; calculated mass for $C_{18}H_{18}N^+$: 248.1434.

The corresponding enantiomer, *(S)-N-(diphenylmethylene)-2-methylbut-3-yn-1-amine [(+)-**13**]*, was made in an analogous manner starting from (*R*)-(−)-Roche ester: $[\alpha]_D$ = +10 (c 0.18, CH_2Cl_2).

*(R,3Z,9Z,11E)-12-(3,5-Dimethoxyphenyl)-1-((diphenylmethylene)amino)-2-methyl-10-(trimethylsilyl)dodeca-3,9,11-trien-5-one [(−)-**14**].* To a solution of alkyne (−)-**13** (2.32 g, 9.38 mmol) in 12 mL THF at −78 °C was added dropwise via syringe LDA (2 M in THF, 4.6 mL, 9.2 mmol) and the resulting mixture was stirred at −78 °C for 1 h before warming up to rt. After stirring at rt for another 1 h, the reaction was recooled to −78 °C and transferred via cannula to a solution of aldehyde **8** (1.45 g, 4.36 mmol) in 10 mL THF at −78 °C. The resulting solution was stirred at −78 °C for 5 h, then warmed to rt and quenched with solid NH_4Cl. This resulting mixture was filtered, concentrated *in vacuo*, and purified by flash chromatography (1% Et_3N in 15% EtOAc/hexane) to provide 44% recovery of alkyne **13** along with a diastereomeric mixture of propargylic alcohols (2.43 g, 4.19 mmol, 96%) as a yellow oil: R_f = 0.35 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, C_6D_6) δ 7.88 (dd, J = 6.6, 2.8 Hz, 2H), 7.15−7.04 (m, 6H), 7.01−6.94 (m, 3H), 6.78 (d, J = 2.2 Hz, 2H), 6.62 (d, J = 15.8 Hz, 1H), 6.51 (t, J = 2.2 Hz, 1H), 6.34 (dd, J = 7.7, 6.6 Hz, 1H), 4.27 (t, J = 5.5 Hz, 2H), 3.61 (ddd, J = 13.5, 6.0, 1.1 Hz, 1H), 3.43 (dd, J = 13.5, 7.2 Hz, 1H), 3.36 (s, 6H), 3.11−3.01 (m, 1H), 2.22−2.10 (m, 2H), 1.77−1.54 (m, 4H), 1.29 (d, J = 6.9 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 168.6, 161.8, 145.5, 140.9, 140.3, 138.9, 137.4, 135.7, 130.3, 129.0, 128.8, 128.5, 128.2, 127.9, 105.3, 104.9, 99.9, 88.6, 83.2, 62.5, 59.7, 54.9, 38.2, 32.2, 28.7, 26.1, 19.4, 0.8; HRMS (E+) m/z 580.3245 $(M+H)^+$; calculated mass for $C_{37}H_{46}NO_3Si^+$: 580.3242.

The resulting diastereomeric mixture of alcohols (1.47 g, 2.53 mmol) was combined with *N*-methylmorpholine *N*-oxide (890 mg, 7.59 mmol, 3 equiv) in 17 mL CH_2Cl_2 at rt. To this stirred solution was added over 30 min tetra-*n*-propylammonium perruthenate (220 mg, 0.63 mmol, 25 mol %) and the resulting mixture was stirred at rt for 24 h. The reaction was then diluted with 20 mL hexane and filtered through a plug of silica gel eluting with 50% CH_2Cl_2/hexanes. The resulting filtrate was concentrated *in vacuo* and further purified by flash chromatography (1% Et_3N in 15% Et_2O/hexane) to afford the corresponding alkynone (1.16 g, 2.01 mmol, 79%) as a pale yellow oil: R_f = 0.59 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, C_6D_6) δ 7.86 (dd, J = 6.5, 3.0 Hz, 2H), 7.15−7.04 (m, 6H), 6.98−6.91 (m, 3H), 6.78 (d, J = 2.1 Hz, 2H), 6.60 (d, J = 15.8 Hz, 1H), 6.51 (t, J = 2.0 Hz, 1H), 6.22 (dd, J = 7.6, 6.8 Hz, 1H), 3.48−3.39 (m, 1H), 3.36 (s, 6H), 3.35−

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3.29 (m, 1H), 2.93 (h, J = 6.8 Hz, 1H), 2.38 (dt, J = 14.5, 7.1 Hz, 2H), 2.11 (dd, J = 15.0, 7.5 Hz, 2H), 1.75−1.64 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 186.4, 169.0, 161.8, 144.5, 140.8, 140.1, 139.7, 137.1, 135.5, 130.4, 128.96, 128.87, 128.6, 128.5, 128.4, 127.98, 104.9, 100.0, 96.1, 82.1, 58.5, 54.9, 45.2, 31.5, 28.8, 24.5, 18.1, 0.7; IR (thin film) ν 2954, 2210, 1672, 1622, 1591, 1455; $[\alpha]_D$ = −6 (c 0.4, CH_2Cl_2); HRMS (E+) m/z 578.3076 $(M+H)^+$; calculated mass for $C_{37}H_{44}NO_3Si^+$: 578.3085.

A mixture of the resulting alkynone (1.15 g, 2.00 mmol), Lindlar's catalyst (850 mg, 0.4 mmol Pd, 0.2 equiv), pyridine (2.4 mL, 15 equiv), and toluene (20 mL) was stirred vigorously at rt under a H_2 atmosphere (balloon) for 24 h. **NOTE**: TLC never showed completion even after 48 h. The resulting mixture was filtered through Celite, concentrated *in vacuo*, and purified by flash chromatography (1% Et_3N in 10% EtOAc/hexane) to provide enone (−)-**14** (900 mg, 1.55 mmol, 78%) as a pale yellow oil: R_f = 0.54 (15% EtOAc/hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.86 (dd, J = 6.7, 2.9 Hz, 2H), 7.14−7.06 (m, 6H), 7.00 (d, J = 15.8 Hz, 1H), 6.93 (d, J = 6.4 Hz, 2H), 6.80 (d, J = 2.1 Hz, 2H), 6.65 (d, J = 15.8 Hz, 1H), 6.52 (t, J = 2.1 Hz, 1H), 6.32 (t, J = 7.4 Hz, 1H), 6.04−5.98 (m, 1H), 5.89 (d, J = 11.5 Hz, 1H), 4.25−4.14 (m, 1H), 3.41 (dd, J = 5.4, 4.0 Hz, 2H), 3.35 (s, 6H), 2.28−2.15 (m, 4H), 1.78−1.66 (m, 2H), 1.17 (d, J = 6.7 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 199.8, 168.0, 161.8, 152.1, 145.1, 140.8, 140.4, 139.4, 137.5, 135.6, 130.1, 128.9, 128.7, 128.5, 128.2, 127.9, 126.2, 105.3, 104.9, 100.0, 59.7, 54.9, 43.6, 35.3, 31.8, 24.4, 18.6, 0.8; IR (thin film) ν 2955, 1690, 1592, 1381; $[\alpha]_D$ = −69.5 (c 0.2, CH_2Cl_2); HRMS (E+) m/z 580.3243 $(M+H)^+$; calculated mass for $C_{37}H_{46}NO_3Si^+$: 580.3242.

General Procedure for the Lewis Acid-Mediated IMDA Cycloaddition of Trienone (−)-14. To a solution of (*Z*)-enone (−)-**14** (60 mg, 103 μmol) in 2 mL CH_2Cl_2 at the indicated temperature (Table 1) was added via syringe Me_2AlCl (0.9 M in heptane, 130 μL, 1.12 equiv) and the resulting yellow solution was stirred at the indicated temperature for the indicated amount of time (Table 1). The reaction was then quenched with saturated aq $NaHCO_3$ (5 mL), extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow residue was purified by flash chromatography (1% Et_3N in 10% EtOAc/hexane) to provide cycloaddition product (−)-**16** as white solid plus varying amounts of the (*E*)-enone (−)-**15**. The diastereomeric ratio for (−)-**16** versus the corresponding *endo* adduct was determined by ^{1}H NMR analysis of the crude reaction mixture prior to chromatography. When the reaction was conducted exclusively at −78 °C, only the starting material plus (*E*)-enone **15** were isolated. When the reaction was conducted at −78 °C and warmed up to −30 °C over 12h, **16** was the only cycloaddition product observed ($dr \geq$ 20:1), albeit in 43% isolated yield. The isolated yield for cycloaddition adduct **16** increased with reaction temperature (64% at 20 °C) at the expense of diastereoselectivity (12:1 *exo*:*endo* at 20 °C).

*(R,3E,9Z,11E)-12-(3,5-Dimethoxyphenyl)-1-((diphenylmethylene)-amino)-2-methyl-10-(trimethylsilyl)dodeca-3,9,11-trien-5-one [(−)-**15**].* The (*E*)-enone (−)-**15** was frequently isolated as a minor product to the above cycloaddition reaction: Pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 7.89−7.80 (m, 2H), 7.15−7.03 (m, 6H), 6.99 (d, J = 15.7 Hz, 1H), 6.94−6.86 (m, 3H), 6.81−6.77 (m, 2H), 6.64 (dd, J = 15.8, 2.7 Hz, 1H), 6.52−6.49 (m, 1H), 6.33 (t, J = 7.6 Hz, 1H), 6.14−6.08 (m, 1H), 3.37−3.34 (m, 6H), 3.34−3.24 (m, 2H), 2.74−2.58 (m, 1H), 2.35−2.26 (m, 2H), 2.21 (dd, J = 14.9, 7.5 Hz, 2H), 1.82−1.70 (m, 2H), 1.04−0.99 (d, J = 6.8 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 198.5, 168.3, 161.8, 150.0, 145.1, 140.8, 140.2, 139.4, 137.4, 135.6, 130.3, 129.6, 128.8, 128.5,128.4, 128.2, 127.9, 105.3, 104.9, 100.0, 59.1, 54.9, 39.7, 38.7, 31.9, 24.5, 17.5, 0.8; IR (thin film) ν 3442, 2956, 1591, 1381; $[\alpha]_D$ = −4.3 (c 0.49, CH_2Cl_2); HRMS (E+) m/z 580.3233 $(M+H)^+$; calculated mass for $C_{37}H_{46}NO_3Si^+$: 580.3242.

*(4aR,7S,8S,8aS)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((diphenylmethylene)amino)propan-2-yl)-5-(trimethylsilyl)-2,3,4,4a,8,8a-hexahydronaphthalen-1(7H)-one [(−)-**16**].* White solid: R_f = 0.38 (15% EtOAc/hexane); mp 70−75 °C; NMR data, including 2D NMR correlations, are summarized in Table S1 in the Supporting Information; IR (thin film) ν 3414, 2951, 1712, 1599, 1460, 1154; $[\alpha]_D$ = −81 (c 0.53, CH_2Cl_2); HRMS (E+) m/z 580.3237 $(M+H)^+$; calculated mass for $C_{37}H_{46}NO_3Si^+$: 580.3242.

*(4aS,7R,8S,8aR)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((diphenylmethylene)amino)propan-2-yl)-2,3,4,4a,8,8a-hexahydronaphthalen-1(7H)-one [(−)-**17**].* To a solution of (−)-**16** (50 mg, 86 μmol) and 5 mL CH_3CN at rt in a Nalgene screw-cap plastic bottle was added 50% aqueous HBF_4 (1.1 mL). The resulting solution was heated to 55 °C and stirred at that temperature for 12 h. After cooling to rt, the reaction was quenched with saturated aq $NaHCO_3$ (15 mL) and stirred for 20 min before extracting with EtOAc (3 × 15 mL) and drying ($MgSO_4$). The resulting product was purified by flash chromatography (1% Et_3N in 10% EtOAc/hexane) to provide alkene (−)-**17** (39 mg, 77 μmol, 89%) as a white solid: R_f = 0.37 (1% Et_3N in 10% EtOAc/hexanes); mp 50−53 °C; NMR data, including 2D NMR correlations, are summarized in Table S2 in the Supporting Information; IR (thin film) ν 3443, 2930, 1713, 1598, 1461, 1155; $[\alpha]_D$ = −165 (c 0.49, CH_2Cl_2); HRMS (E+) m/z 508.2842 $(M+H)^+$; calculated mass for $C_{34}H_{38}NO_3^+$: 508.2847.

*(3R,3aS,3a1R,4R,6aS)-4-(3,5-Dimethoxyphenyl)-3-methyl-3,3a,3a1,4,6a,7,8,9-octahydro-2H-benzo[de]quinoline [(−)-**18**].* To a solution of (−)-**17** (99 mg, 195 μmol) in 10 mL THF at rt was added 0.5 M aq TFA (2 mL). The reaction was warmed to 50 °C and stirred at that temperature for 4 h. After cooling to rt, the reaction was then quenched with saturated aq $NaHCO_3$ (20 mL) and stirred for 30 min before extracting with EtOAc (3 × 20 mL) and drying ($MgSO_4$). The resulting product was purified by flash chromatography (1% Et_3N/EtOAc) to provide imine (−)-**18** (60 mg, 184 μmol, 95%) as a yellow oil: R_f = 0.38 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, J = 2.1 Hz, 2H), 6.35 (t, J = 2.2 Hz, 1H), 5.74 (d, J = 9.9 Hz, 1H), 5.58 (ddd, J = 9.9, 4.1, 2.3 Hz, 1H), 3.78 (s, 6H), 3.57 (dd, J = 16.4, 2.7 Hz, 1H), 3.48−3.39 (m, 2H), 2.39 (dd, J = 7.9, 6.1 Hz, 1H), 2.27−2.17 (m, 2H), 2.07−1.88 (m, 5H), 1.70−1.55 (m, 1H), 1.45 (qd, J = 12.6, 3.4 Hz, 1H), 0.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 160.8, 144.4, 131.9, 129.5, 109.0, 98.2, 59.5, 55.4, 46.1, 42.9, 41.6, 38.7, 37.6, 32.1, 29.0, 26.5, 12.1;; IR (thin film) ν 3435, 2927, 1656, 1605, 1594, 1459; $[\alpha]_D$ = −221 (c 0.43, CH_2Cl_2); HRMS (E+) m/z 326.2109 $(M+H)^+$; calculated mass for $C_{21}H_{28}NO_2^+$: 326.2115.

*5-((3R,3aR,3a1S,4S,6aR)-3-Methyl-3,3a,3a1,4,6a,7,8,9-octahydro-2H-benzo[de]quinolin-4-yl)benzene-1,3-diol [(−)-**19**].* To a solution of (−)-**18** (29.5 mg, 91 μmol) in 8 mL CH_2Cl_2 at 0 °C was added BBr_3 (1 M in CH_2Cl_2, 0.45 mL, 5 equiv). After stirring at 0 °C for 2.5 h, the reaction was quenched with saturated aq $NaHCO_3$ (10 mL), extracted with 3% MeOH/EtOAc (3 × 10 mL), dried (Na_2SO_4), and purified by gradient flash chromatography (10% MeOH/$CHCl_3$ → 15% MeOH/$CHCl_3$) to provided bisphenol (−)-**19** (26.5 mg, 89 μmol, 98%) as a white solid: R_f = 0.43 (15% MeOH/$CHCl_3$); mp >280 °C; NMR data, including 2D NMR correlations, are summarized in Table S3 in Supporting Information; IR (thin film) ν 3444, 1637; $[\alpha]_D$ = −108 (c 0.012, $CHCl_3$); HRMS (E+) m/z 298.1807 $(M+H)^+$; calculated mass for $C_{19}H_{24}NO_2^+$: 298.1802.

*(R)-Propyl 6,6-dibromo-3-methylhex-5-enoate [(+)-**21**].* To a solution of (*R*)-3-methyl-5-oxo-5-propoxypentanoic acid[19] (92%ee, 7.6 g, 40 mmol) in THF (133 mL) at 0 °C was added via syringe BH_3•DMS (4.0 mL, 44 mmol, 1.1 equiv). The resulting solution was allowed to warm to rt and stirred at that temperature for 15 h. The resulting solution was concentrated *in vacuo* and H_2O (2 mL) was added slowly followed by 1:1 EtOAc/hexane (40 mL). The resulting mixture was stirred at rt for 15 min after which the mixture was filtered through a plug of SiO_2 eluting with 1:1 EtOAc/hexane (300 mL), and concentrated to provide the corresponding alcohol as a colorless oil (7.1 g, 40 mmol, quantitative), which was carried on directly to the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (t, J = 6.7 Hz, 2H), 2.52−2.35 (m, 3H), 2.34−2.21 (m, 2H), 1.73−1.53 (m, 2H), 1.05 (d, J = 6.5 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H).

To a solution of the crude alcohol, NMO•H_2O (7.03 g, 60 mmol, 1.5 equiv), and crushed 4 Å molecular sieves (~10 g) in CH_2Cl_2 (250 mL) and MeCN (10 mL) at rt was added TPAP (350 mg, 2.5 mol %)

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and the reaction was stirred for 3 h when TLC (30% EtOAc/hexane) showed completion. The mixture was diluted with hexane (250 mL), filtered through a plug of SiO_2 eluting with Et_2O (300 mL), and carefully concentrated *in vacuo* without heating the water bath to give the expectant aldehyde as a light purple oil (6.8 g) that was carried on directly to the next step without further purification: R_f = 0.57 (30% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, J = 1.9 Hz, 1H), 4.02 (t, J = 6.7 Hz, 2H), 2.60−2.49 (m, 2H), 2.37−2.24 (m, 3H), 1.64 (tq, J = 11.6, 4.9 Hz, 2H), 1.03 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H).

The aldehyde was then combined with CBr_4 (17.2 g, 52 mmol, 1.3 equiv) in CH_2Cl_2 (400 mL) and cooled to −20 °C before adding PPh_3 (28.3 g, 108 mmol, 2.7 equiv) in portions over 20 min. The reaction was allowed to stir at −20 °C for 4 h before TLC (20% Et_2O/hexane) showed completion. The mixture was then diluted with hexane (400 mL), filtered through a plug of SiO_2 eluting with 20% EtOAc/hexane (400 mL), and concentrated to afford (+)-**21** (10.1 g, 77% over three steps, ∼ 90% purity) as a light yellow oil. An analytical sample was purified by radial chromatography (5% Et_2O/hexane) to give a colorless oil: R_f = 0.30 (5% Et_2O/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (t, J = 7.2 Hz, 1H), 4.03 (t, J = 6.7 Hz, 2H), 2.35−2.27 (m, 1H), 2.21−2.10 (m, 2H), 2.09−2.01 (m, 2H), 1.70−1.60 (m, 2H), 0.99 (d, J = 6.3 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 136.5, 90.0, 66.0, 40.9, 39.6, 29.7, 21.9, 19.6, 10.4; IR (thin film) ν 2964, 2877, 1732, 1619; $[\alpha]_D$ = +9.2 (c 1.0, $CHCl_3$); HRMS (E+) m/z 350.9374 $(M+Na)^+$; calculated mass for $C_{10}H_{16}Br_2NaO_2^+$: 350.9389.

*(R)-3-Methyl-6-(trimethylsilyl)hex-5-yn-1-ol [(+)-**22**].* To a solution of ester (+)-**21** (1.54 g, 4.69 mmol) in 40 mL CH_2Cl_2 at −15 °C was added DIBAL (1 M in hexane, 12 mL, 2.56 mmol) and the resulting reaction mixture was allowed to warm to 25 °C over 5 h. The reaction was then quenched with 1 M aq Rochelle's salt (30 mL) and stirred for 30 min before extracting with Et_2O (3 × 50 mL), drying ($MgSO_4$), and concentrating *in vacuo*. The resulting product was purified by flash chromatography (25% EtOAc/hexane) to provide the expectant primary alcohol (1.21 g, 4.45 mmol, 95%) as a colorless oil: R_f = 0.55 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (t, J = 7.3 Hz, 1H), 3.80−3.59 (m, 2H), 2.12 (ddd, J = 13.2, 7.0, 0.9 Hz, 1H), 2.00 (dtd, J = 8.2, 7.4, 0.7 Hz, 1H), 1.85−1.73 (m, 1H), 1.67−1.56 (m, 1H), 1.56−1.36 (m, 2H), 0.95 (dd, J = 6.7, 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 89.5, 60.9, 40.3, 39.2, 29.3, 19.6; IR (thin film) ν 3335, 2957, 2927, 1457; $[\alpha]_D$ + 3 (c 0.4, CH_2Cl_2).

To a solution of the resulting vinyl dibromide (1.216 g, 4.47 mmol) in THF (20 mL) at −78 °C was added via syringe *n*-BuLi (1.6 M solution in hexane, 8.5 mL, 3.2 equiv). The resulting solution was allowed to warm to rt and was stirred at that temperature for 30 min. The reaction mixture was then cooled back to −78 °C, Me_3SiCl (1.4 mL, 11 mmol, 1.6 equiv) was added via syringe, and the resulting mixture was allowed to warm to rt over 4 h. 5% aq acetic acid (12 mL) was added and the mixture was stirred vigorously for 30 min at rt before extracting with Et_2O (3 × 50 mL). The organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography (15% EtOAc/hexane) to provide TMS-alkyne (+)-**22** (760 mg, 4.12 mmol, 92% over two steps) as a colorless oil: R_f = 0.38 (15% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (qt, J = 10.7, 6.6 Hz, 2H), 2.28−2.11 (m, 2H), 2.08 (s, 1H), 1.92−1.79 (m, 1H), 1.68 (td, J = 13.2, 6.6 Hz, 1H), 1.50 (td, J = 13.9, 6.6 Hz, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.1, 86.0, 61.1, 38.9, 29.5, 27.3, 19.8, 0.3; IR (thin film) ν 3352, 2960, 2928, 2173, 1250; $[\alpha]_D$ + 7 (c 0.3, CH_2Cl_2); HRMS (E+) m/z 185.1364 $(M+H)^+$; calculated mass for $C_{10}H_{21}OSi^+$: 185.1357.

*(R,E)-6-Iodo-3-methyl-6-(trimethylsilyl)hex-5-en-1-ol [(+)-**23**].* To a solution of alkynol (+)-**22** (710 mg, 3.85 mmol) in Et_2O (20 mL) at 0 °C was added via syringe DIBAL (1 M in hexane, 10 mL, 2.6 equiv). The resulting solution was heated to reflux (70 °C) and stirred at that temperature for 24 h. The solution was then cooled to −78 °C, after which a solution of I_2 (4 g, 15.76 mmol, 4 equiv) in Et_2O (60 mL) was added dropwise by addition funnel. After stirring at −78 °C for 2 h, the reaction was carefully quenched by pouring into 1 M HCl (30 mL). The maroon organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed sequentially with saturated aq $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by column chromatography (15% EtOAc/hexane) to yield vinyl iodide (+)-**23** (865 mg, 2.77 mmol, 72%) as a pale yellow oil: R_f = 0.38 (15% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, J = 7.9 Hz, 1H), 3.76−3.61 (m, 2H), 2.17−2.05 (m, 1H), 2.03−1.92 (m, 1H), 1.78−1.56 (m, 2H), 1.45−1.31 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 107.8, 61.0, 42.3, 39.4, 29.9, 19.5, 1.4; IR (thin film) ν 3349, 2957, 2927, 1250, 844; $[\alpha]_D$ + 3.3 (c 0.36; CH_2Cl_2); HRMS (E+) m/z 335.0288 $(M+Na)^+$; calculated mass for $C_{10}H_{21}IONaSi^+$: 335.0299.

*(R,5Z,7E)-8-(3,5-Dimethoxyphenyl)-3-methyl-6-(trimethylsilyl)-octa-5,7-dien-1-ol [(+)-**24**].* Vinyl iodide (+)-**23** (770 mg, 2.47 mmol) and pinacol boronate **6** (1.07 g, 3.69 mmol, 1.5 equiv) were combined in THF (10 mL) and deionized H_2O (2.5 mL). Argon was bubbled through the solution for 30 min, then KOH (208 mg, 3.7 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (715 mg, 0.62 mmol, 25 mol %) were added and the resulting mixture was heated to 50 °C and stirred at that temperature for 8 h. After cooling to rt, the reaction was diluted with EtOAc (50 mL), washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc/hexane) to give the desired diene (560 mg, 1.61 mmol, 65%) as a pale brown oil: R_f = 0.25 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, J = 15.8, 0.9 Hz, 1H), 6.54 (d, J = 2.2 Hz, 2H), 6.38 (d, J = 15.8 Hz, 1H), 6.35−6.32 (m, 2H), 3.80 (s, 6H), 3.78−3.65 (m, 2H), 2.33−2.20 (m, 1H), 2.18−2.07 (m, 1H), 1.80−1.64 (m, 2H), 1.50−1.38 (m, 1H), 1.34 (s, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 144.0, 140.4, 139.5, 135.6, 127.4, 104.6, 104.3, 100.1, 99.3, 61.2, 55.4, 39.7, 39.4, 30.7, 19.8, 0.8; IR (thin film) ν 3381, 2955, 1592, 1459; $[\alpha]_D$ + 1.2 (c 0.33, CH_2Cl_2); HRMS (E+) m/z 349.2200 $(M+H)^+$; calculated mass for $C_{20}H_{33}O_3Si^+$: 349.2194.

To a solution of the resulting alcohol (475 mg, 1.36 mmol) in DMSO (8 mL) was added in one portion IBX (575 g, 2.05 mmol, 1.5 equiv) and the reaction was stirred at rt for 4 h. The resulting mixture was then diluted with saturated aq $NaHCO_3$/H_2O and extracted with Et_2O. The combined organic extract was washed with 5% aq LiCl, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography (15% Et_2O/hexane) to give aldehyde (+)-**24** (410 mg, 1.18 mmol, 87%) as a pale yellow oil: R_f = 0.53 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, J = 1.9 Hz, 1H), 6.78 (d, J = 15.8 Hz, 1H), 6.54 (d, J = 2.2 Hz, 2H), 6.38 (d, J = 15.7 Hz, 1H), 6.34 (t, J = 2.2 Hz, 1H), 6.30 (dd, J = 7.2, 6.1 Hz, 1H), 3.80 (s, 6H), 2.53−2.47 (m, 1H), 2.32−2.16 (m, 4H), 1.03 (d, J = 6.0 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 161.0, 142.5, 140.6, 140.2, 135.3, 127.7, 104.3, 99.4, 55.4, 50.6, 38.9, 29.1, 20.2, 0.8; IR (thin film) ν 2956, 2837, 2719, 1724, 1591; $[\alpha]_D$ + 5.9 (c 0.27, CH_2Cl_2); HRMS (E+) m/z 369.1850 $(M+Na)^+$; calculated mass for $C_{20}H_{30}NaO_3Si^+$: 369.1857.

*(2R,3Z,7R,9Z,11E)-12-(3,5-Dimethoxyphenyl)-1-((diphenylmethylene)amino)-2,7-dimethyl-10-(trimethylsilyl)-dodeca-3,9,11-trien-5-one [(−)-**25**].* To a solution of alkyne (−)-**13** (630 mg, 2.55 mmol, 2.15 equiv) in THF (10 mL) at −78 °C was added dropwise via syringe LDA (2 M in THF, 1.25 mL, 2.5 mmol). The mixture was stirred at −78 °C for 1h before warming to rt. After stirring for 1 h at rt, the reaction was cooled back to −78 °C and transferred via cannula to a stirred solution of aldehyde (+)-**24** (410 mg, 1.18 mmol) in THF (10 mL) at −78 °C. The resulting solution was stirred at −78 °C for 7 h, then warmed to rt, quenched with solid NH_4Cl, filtered, concentrated, and purified via flash chromatography (1% Et_3N in 15% EtOAc/hexane) to give the diastereomeric mixture of intermediate propargyl alcohols (673 mg, 1.13 mmol, 96%) as a yellow oil. The starting alkyne (−)-**13** was recovered in 49% yield: ^{1}H NMR (400 MHz, C_6D_6) δ 7.92−7.86 (m, 2H), 7.14−7.02 (m, 7H), 7.00−6.95 (m, 2H), 6.79 (d, J = 2.2 Hz, 2H), 6.65 (d, J = 15.7 Hz, 1H), 6.52 (t, J = 2.1 Hz, 1H), 6.42 (ddd, J = 7.5, 4.6, 2.3 Hz, 1H), 4.38 (dd, J = 14.1, 6.9 Hz, 1H), 3.62 (ddd, J = 13.5, 7.4, 6.1 Hz, 1H), 3.44

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(ddd, J = 13.5, 7.3, 3.5 Hz, 1H), 3.35 (s, 6H), 3.07 (qd, J = 6.8, 3.4 Hz, 1H), 2.26 (ddd, J = 17.8, 13.4, 6.0 Hz, 1H), 2.11−1.93 (m, 2H), 1.91−1.70 (m, 1H), 1.65−1.46 (m, 2H), 1.28 (d, J = 6.9 Hz, 3H), 0.89 (dd, J = 6.5, 1.3 Hz, 3H), 0.25 (d, J = 1.2 Hz, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 168.5, 161.8, 144.5, 140.9, 140.3, 139.7, 139.6, 137.4, 135.8, 130.3, 129.0, 128.8, 128.5, 128.2, 127.9, 104.9, 99.9, 61.2, 59.6, 54.9, 45.8, 45.6, 39.5, 31.1, 28.7, 19.9, 19.6, 19.4, 0.9; HRMS (E+) m/z 594.3401 $(M+H)^+$; calculated mass for $C_{38}H_{48}NO_3Si^+$: 594.3398.

The resulting diastereomeric mixture of alcohols was combined with NMO (408 mg, 3.48 mmol, 3 equiv) in CH_2Cl_2 (10 mL) at rt. To the resulting solution was added in portions over 30 min TPAP (102 mg, 0.29 mmol, 25 mol %) and the mixture was stirred at rt for 24 h. The resulting reaction mixture was diluted with hexane (10 mL) and filtered through a plug of silica gel eluting with 50% CH_2Cl_2/hexane. The solution was concentrated and further purified by flash chromatography (1% Et_3N in 8% EtOAc/hexane) to afford the corresponding ketone (495 mg, 0.84 mmol, 72%) as a yellow oil: R_f = 0.26 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.86 (dd, J = 6.6, 3.0 Hz, 2H), 7.14−7.03 (m, 6H), 6.97 (d, J = 15.2 Hz, 1H), 6.95−6.91 (m, 2H), 6.79 (d, J = 2.1 Hz, 2H), 6.62 (d, J = 15.8 Hz, 1H), 6.52 (t, J = 2.1 Hz, 1H), 6.30 (dtj, J = 7.5, 1.0 Hz, 1H), 3.46−3.39 (m, 1H), 3.35 (s, 6H), 3.34−3.28 (m, 1H), 2.97−2.88 (m, 1H), 2.47 (dd, J = 14.9, 5.1 Hz, 1H), 2.34 (dt, J = 9.5, 5.2 Hz, 1H), 2.27 (dd, J = 14.9, 7.8 Hz, 1H), 2.19 (dd, J = 13.8, 7.0 Hz, 1H), 2.04 (dt, J = 14.8, 7.5 Hz, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 186.4, 169.0, 161.8, 143.4, 140.8, 140.4, 140.0, 137.1, 135.6, 130.4, 128.95, 128.87, 128.56, 128.53, 128.35, 127.97, 104.9, 100.0, 96.1, 82.4, 58.5, 54.9, 52.8, 39.0, 30.7, 28.8, 19.8, 18.1, 0.8; IR (thin film) ν 2957, 2211, 1670, 1622, 1592; $[\alpha]_D$ − 1.5 (c 0.2, CH_2Cl_2); HRMS (E+) m/z 592.3244 $(M+H)^+$; calculated mass for $C_{38}H_{46}NO_3Si^+$: 592.3242.

A mixture of the resulting alkynone (140 mg, 0.24 mmol), Lindlar catalyst (103 mg, 48.4 μmol Pd, 20 mol %), pyridine (0.28 mL, 3.47 mmol, 14.6 equiv), and toluene (5 mL) were stirred vigorously at rt under a H_2 atmosphere (balloon) for 24 h. The mixture was then filtered through Celite, concentrated *in vacuo*, and purified by flash chromatography (1% Et_3N in 8% EtOAc/hexane) to provide *cis*-enone (−)-**25** (96 mg, 0.16 mmol, 68%) as a pale yellow oil: R_f = 0.37 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.90−7.81 (m, 2H), 7.15−7.05 (m, 6H), 7.02 (d, J = 15.9 Hz, 1H), 6.94−6.89 (m, 2H), 6.80 (t, J = 2.0 Hz, 2H), 6.66 (dd, J = 15.7, 1.3 Hz, 1H), 6.52 (dd, J = 4.1, 2.0 Hz, 1H), 6.38 (t, J = 7.2 Hz, 1H), 6.01 (dd, J = 11.0, 10.0 Hz, 1H), 5.92 (d, J = 11.5 Hz, 1H), 4.24−4.12 (m, 1H), 3.41 (d, J = 5.9 Hz, 2H), 3.34 (s, 6H), 2.33 (dd, J = 15.4, 4.8 Hz, 1H), 2.25 (dd, J = 16.2, 6.0 Hz, 2H), 2.15−2.05 (m, 2H), 1.17 (dd, J = 6.7, 1.3 Hz, 3H), 0.94 (d, J = 6.0 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 199.8, 168.0, 161.8, 152.2, 144.0, 140.8, 140.4, 140.0, 137.5, 135.7, 130.1, 128.9, 128.7, 128.5, 127.9, 126.5,104.9, 100.0, 64.8, 59.7, 54.8, 51.2, 39.3, 35.3, 30.5, 20.1, 18.6, 14.4, 0.9; IR (thin film) ν 3438, 2957, 1689, 1592; $[\alpha]_D$ − 54 (c 0.41, CH_2Cl_2); HRMS (E+) m/z 594.3396 $(M+H)^+$; calculated mass for $C_{38}H_{48}NO_3Si^+$: 594.3398.

*(2S,3Z,7R,9Z,11E)-12-(3,5-Dimethoxyphenyl)-1-((diphenylmethylene)amino)-2,7-dimethyl-10-(trimethylsilyl)-dodeca-3,9,11-trien-5-one [(+)-**26**].* To a solution of alkyne (+)-**13** (1.21 g, 4.89 mmol, 2.07 equiv) in THF (10 mL) at −78 °C was added dropwise via syringe LDA (2 M in THF, 2.45 mL, 4.9 mmol). The mixture was stirred at −78 °C for 1 h before warming to rt. After stirring for 1 h at rt, the reaction was cooled back to −78 °C and transferred via cannula to a stirred solution of aldehyde (+)-**24** (820 mg, 2.37 mmol) in THF (7 mL) at −78 °C. The resulting solution was stirred at −78 °C for 7 h, then warmed to rt, quenched with solid NH_4Cl, filtered, concentrated, and purified via flash chromatography (1% Et_3N in 15% EtOAc/hexane) to give the intermediate propargyl alcohol (1.25 g, 2.10 mmol, 89%) as a yellow oil. The starting alkyne (+)-**13** was recovered in 45% yield.

The resulting diastereomeric mixture of alcohols (1.23 g, 2.07 mmol) was combined with NMO (735 mg, 6.27 mmol, 3 equiv) in CH_2Cl_2 (30 mL) at rt. To the resulting solution was added in portions over 30 min TPAP (180 mg, 0.51 mmol, 25 mol %) and the mixture was stirred at rt for 24 h. The resulting reaction mixture was diluted with hexane (30 mL) and filtered through a plug of silica gel eluting with 50% CH_2Cl_2/hexane. The solution was concentrated and further purified by flash chromatography (1% Et_3N in 8% EtOAc/hexane) to afford the desired ketone (1.05 g, 1.77 mmol, 86%) as a yellow oil.

A mixture of the resulting alkynone (154 mg, 0.26 mmol), Lindlar catalyst (110 mg, 51.7 μmol Pd, 20 mol %), pyridine (0.42 mL, 52 mmol, 20 equiv), and toluene (8 mL) were stirred vigorously at rt under a H_2 atmosphere (balloon) for 17 h. The mixture was then filtered through Celite, concentrated *in vacuo*, and purified by flash chromatography (1% Et_3N in 8% EtOAc/hexane) to provide *cis*-enone (+)-**26** (107 mg, 0.18 mmol, 69%) as a pale yellow oil: R_f = 0.49 (15% EtOAc/hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.90−7.81 (m, 2H), 7.15−7.05 (m, 6H), 7.01 (d, J = 15.7 Hz, 1H), 6.95−6.90 (m, 2H), 6.79 (t, J = 2.1 Hz, 2H), 6.66 (d, J = 15.8 Hz, 1H), 6.51 (t, J = 2.2 Hz, 1H), 6.40 (t, J = 6.8 Hz, 1H), 6.01 (dd, J = 11.5, 9.5 Hz, 1H), 5.92 (d, J = 11.5 Hz, 1H), 4.28−4.12 (m, 1H), 3.42 (d, J = 6.5 Hz, 2H), 3.35 (s, 6H), 2.40−2.04 (m, 5H), 1.16 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.2 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 199.8, 168.0, 161.8, 152.1, 143.9, 140.8, 140.4, 140.1, 137.6, 135.7, 130.1, 128.89, 128.73, 128.50, 128.18, 127.94, 126.6, 104.9, 100.0, 59.7, 54.9, 51.2, 39.3, 35.3, 30.5, 20.1, 18.6, 0.9; IR (thin film) ν 3374, 2928, 1688, 1577.9, 1453, 1407; $[\alpha]_D$ + 74.5 (c 0.11, CH_2Cl_2); HRMS (E+) m/z 594.3411 $(M+H)^+$; calculated mass for $C_{38}H_{48}NO_3Si^+$: 594.3398.

IMDA Cyclization of (−)-25. To a solution of (*Z*)-enone (−)-**25** (35 mg, 59 μmol) in CH_2Cl_2 (2.5 mL) at −20 °C was added via syringe Me_2AlCl (0.9 M in heptane, 0.1 mL, 1.5 equiv) and the resulting yellow solution was stirred at −20 °C for 5 h. The reaction was then quenched with saturated aq $NaHCO_3$ (5 mL), extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Crude ^{1}H NMR analysis showed the IMDA adducts **27**:**28**:**29** were produced in a ratio of 1:3:2.9 (exo:endo =1.4), respectively. Purification by repetitive flash chromatography (1% Et_3N in 8% EtOAc/hexane) afforded the *exo* products **27** and **28** in a 1:3 ratio, as determined by ^{1}H NMR analysis (21 mg, 35.4 μmol, 60%) and (+)-**29** (9 mg, 26%). **Note:** Using Lewis acid $BF_3{\cdot}Et_2O$ at 0 °C can switch the initial selectivity of *exo* adducts **27** and **28** (**27**:**28** = 1.55:1 ratio) and barely no **29** (*exo*:*endo* > 12). Serial chromatography of the *exo*-product mixture could improve the ratio to 4:1 in favor of **27**. Comparative 1D-NMR analysis of 1:1 and 4:1 mixtures allowed for peak correlations for **27** and **28** in the ^{1}H and ^{13}C NMR spectra. 2D-NMR analysis was conducted on a roughly 1:1 mixture of **27**:**28** to determine the absolute stereochemistry of each diastereomer.

*(3R,4aS,7R,8R,8aR)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((diphenylmethylene)amino)propan-2-yl)-3-methyl-5-(trimethylsilyl)-2,3,4,4a,8,8a-hexahydronaphthalen-1(7H)-one (**27**).* Could not be separated completely from diastereomer **28**. R_f = 0.35 (10% EtOAc/hexanes); NMR data, including 2D NMR correlations, summarized in Table S4 in Supporting Information; IR (thin film) ν 3443, 2955, 1711, 1599; HRMS (E+) m/z 594.3393 $(M+H)^+$; calculated mass for $C_{38}H_{48}NO_3SI^+$: 594.3398.

*(3R,4aR,7S,8S,8aS)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((diphenylmethylene)amino)propan-2-yl)-3-methyl-5-(trimethylsilyl)-2,3,4,4a,8,8a-hexahydronaphthalen-1(7H)-one (**28**).* Could not be separated completely from diastereomer **27**. R_f = 0.35 (10% EtOAc/hexanes); NMR data, including 2D NMR correlations, summarized in Table S5 in Supporting Information; HRMS (E+) m/z 594.3393 $(M+H)^+$; calculated mass for $C_{38}H_{48}NO_3SI^+$: 594.3398.

*(3R,4aR,7S,8R,8aR)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((diphenylmethylene)amino)propan-2-yl)-3-methyl-5-(trimethylsilyl)-2,3,4,4a,8,8a-hexahydronaphthalen-1(7H)-one [(+)-**29**].* R_f = 0.37 (12% EtOAc/hexanes); NMR data, including 2D NMR correlations, summarized in Table S6 in Supporting Information; IR (thin film) ν 3444, 2954, 2925, 2859, 1699, 1599; $[\alpha]_D$ + 148 (c 0.15, CH_2Cl_2); HRMS (E+) m/z 594.3393 $(M+H)^+$; calculated mass for $C_{38}H_{48}NO_3SI^+$: 594.3398.

*(3R,4aS,7R,8R,8aR)-7-(3,5-Dimethoxyphenyl)-8-((S)-1-((diphenylmethylene)amino)propan-2-yl)-3-methyl-5-(trimethylsilyl)-2,3,4,4a,8,8a-hexahydronaphthalen-1(7H)-one [(+)-**30**].* To a solution of (*Z*)-enone (+)-**26** (48 mg, 81 μmol) in CH_2Cl_2 (3 mL) at −20 °C was added via syringe Me_2AlCl (0.9 M in heptane, 0.18 mL,

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2 equiv) and the resulting yellow solution was stirred at −20 °C for 4 h. The reaction was then quenched with saturated aq $NaHCO_3$ (5 mL), extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$),concentrated *in vacuo*, and purified by flash chromatography (1% Et_3N in 8% EtOAc/hexane) to afford *exo* product (+)-**30** (34.2 mg, 57.6 μmol, 71%) plus a complex mixture of other compounds (7.8 mg, ∼ 16%) that did not correspond to IMDA cyclization products as determined by ^1H NMR spectroscopic analysis. R_f = 0.35 (10% EtOAc/hexanes); mp 60−64 °C; NMR data, including 2D NMR correlations, summarized in Table S7 in Supporting Information. IR (thin film) ν 3446, 2954, 1711, 1600, 1458, 1154; $[\alpha]_D$ + 158.7 (*c* 0.046,CH_2Cl_2); HRMS (E+) *m*/*z* 594.3412 $(M+H)^+$; calculated mass for $C_{38}H_{48}NO_3SI^+$: 594.3398.

*(R,5Z,7E)-Propyl 6-Bromo-8-(3,5-dimethylphenyl)-3-methyl-octa-5,7-dienoate [(+)-**31**]. Method A.*[25] A mixture of dibromide (+)-**21** (6.01 g, 18.3 mmol), boronate ester **6** (5.76 g, 19.8 mmol, 1.1 equiv) and Tl_2CO_3 (17.1 g, 36.6 mmol, 2.0 equiv) in 4:1 THF/H_2O (180 mL) was degassed by bubbling N_2 through the mixture for 20 min before adding $Pd(PPh_3)_4$ (1.05 g, 0.91 mmol, 5 mol %). The resulting mixture was allowed to stir at rt for 12 h before filtering through a Buchner funnel, diluting with H_2O (150 mL) and extracting with EtOAc (3 × 100 mL). The combined organics were dried ($MgSO_4$), concentrated, and purified by gradient flash chromatography (5 → 15% EtOAc/hexane) to afford diene (+)-**31** (5.33 g, 13.0 mmol, 71%) as a yellow oil.

Method B. A mixture of dibromide (+)-**21** (2.11 g, 6.43 mmol), boronate ester **6** (1.96 g, 6.75 mmol, 1.05 equiv), Cs_2CO_3 (5.24 g, 16.08 mmol, 2.5 equiv), and tri-2-furanylphosphine (TFP, 240 mg, 1.03 mmol, 16 mol %) in 4:1 dioxane/H_2O (25 mL) was degassed by bubbling argon through the mixture for 30 min before adding $Pd_2(dba)_3$ (175 mg, 0.19 mmol, 3 mol %). The resulting reaction mixture was stirred at 30 °C for 12 h and then was diluted with EtOAc (200 mL), washed with brine (3 × 50 mL), dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography (5% EtOAc/hexane) to provide diene (+)-**31** (1.75 g, 66%) as a yellow oil: R_f = 0.47 (10% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 15.1 Hz, 1H), 6.71 (d, *J* = 15.1 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.38 (t, *J* = 2.2 Hz, 1H), 6.09 (t, *J* = 7.2 Hz, 1H), 4.03 (t, *J* = 6.7 Hz, 2H), 3.81 (s, 6H), 2.53−2.28 (m, 3H), 2.28−2.13 (m, 2H), 1.73−1.55 (m, 2H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 161.0, 138.5, 133.2, 132.9, 128.4, 126.7, 104.9, 100.5, 66.1, 55.5, 41.4, 38.7, 30.6, 22.1, 20.0, 10.6; IR (thin film) ν 2962, 2837, 1730, 1590, 1457, 1204, 1154; $[\alpha]_D$ = +6.5 (*c* 0.90, $CHCl_3$); HRMS (E+) *m*/*z* 433.0995 and 435.0964 $(M+Na)^+$; calculated mass for $C_{20}H_{27}BrNaO_4^+$: 433.0985 and 435.0965.

*(R,5E,7E)-8-(3,5-Dimethylphenyl)-3,6-dimethylocta-5,7-dien-1-ol [(+)-**32**].*[25] To a solution of vinyl bromide (+)-**31** (5.0 g, 12.2 mmol) and $Pd[P(t\text{-}Bu)_3]_2$ (75 mg, 0.24 mmol, 2.0 mol %) in THF (80 mL) at 0 °C was added slowly via syringe Me_2Zn (10% w/w in hexane, 12.8 g, 20 mL, 13.4 mmol, 1.5 equiv). After 1 h at 0 °C the reaction was quenched carefully with saturated aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to afford the corresponding methylated diene (4.7 g, > 100%) as a green oil. This crude reaction product was typically carried on directly to the next step without further purification. An analytical sample was purified by radial chromatography to give a colorless oil: R_f = 0.33 (10% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 16.0 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.34 (t, *J* = 2.2 Hz, 1H), 5.65 (t, *J* = 7.2 Hz, 1H), 4.03 (t, *J* = 6.7 Hz, 2H), 3.80 (s, 6H), 2.35 (dd, *J* = 14.5, 5.5 Hz, 1H), 2.27−2.19 (m, 1H), 2.18−2.09 (m, 3H), 1.85 (s, 3H) 1.69−1.59 (m, 2H), 0.99 (d, *J* = 6.2 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 160.8, 139.8, 135.0, 134.2, 131.9, 125.9, 104.1, 99.4, 65.8, 55.2, 41.2, 35.3, 31.0, 21.9, 19.8, 12.5, 10.4; IR (thin film) ν 2962, 2837, 1731, 1590, 1456, 1424, 1328, 1204, 1153, 1063; $[\alpha]_D$ = +4.0 (*c* 0.90, $CHCl_3$).

To a solution of crude ester (4.7 g, ∼ 12.2 mmol) in Et_2O (95 mL) at 0 °C was added in one portion $LiAlH_4$ (0.51 g, 13.4 mmol, 1.1 equiv). After 1 h at 0 °C, 1 M aq Rochelle's salt (100 mL) was added slowly and the mixture stirred for 1 h before extracting with EtOAc (3 × 50 mL), drying ($MgSO_4$) and concentration *in vacuo* to a brown oil (3.8 g). Purification by flash chromatography (10% EtOAc/hexane) afforded alcohol (+)-**32** (3.61 g, 93% over two steps) as a clear colorless oil: R_f = 0.33 (10% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 16.0 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.34 (t, *J* = 2.2 Hz, 1H), 5.66 (t, *J* = 7.5 Hz, 1H), 3.80 (s, 6H), 3.75−3.64 (m, 2H), 2.21 (td, *J* = 13.8, 6.7 Hz, 1H), 2.10 (td, *J* = 14.8, 7.5 Hz, 1H), 1.85 (s, 3H) 1.78−1.62 (m, 2H), 1.46−1.37 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 140.0, 134.6, 134.5, 133.0, 125.7, 104.2, 99.4, 61.1, 55.3, 39.5, 35.9, 30.4, 19.7, 12.6; IR (thin film) ν 3356, 2930, 2836, 1589, 1457, 1424, 1203, 1152, 1062; $[\alpha]_D$ = +3.4 (*c* 1.0, $CHCl_3$); HRMS (E+) *m*/*z* 313.1746 $(M+Na)^+$; calculated mass for $C_{18}H_{26}NaO_3^+$: 313.1775.

*(R,5E,7E)-8-(3,5-Dimethoxyphenyl)-3,6-dimethylocta-5,7-dienal [(+)-**33**].* To a solution of alcohol (+)-**32** (840 mg, 2.89 mmol) in DMSO (12 mL) at rt was added IBX (1.21 g, 4.32 mmol, 1.5 equiv) and the reaction mixture was stirred at rt for 4 h. The resulting mixture was then diluted with saturated aq $NaHCO_3$/H_2O and extracted with Et_2O. The combined organic extract was washed with 5% aq LiCl, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography (25% Et_2O/hexane) to give aldehyde (+)-**33** (734 mg, 2.55 mmol, 88%) as a pale yellow oil: R_f = 0.67 (20% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.57 (d, *J* = 2.1 Hz, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.34 (t, *J* = 2.1 Hz, 1H), 5.63 (t, *J* = 6.7 Hz, 1H), 3.81 (s, 6H), 2.46 (d, *J* = 12.9 Hz, 1H), 2.32−2.14 (m, 4H), 1.85 (s, 3H), 1.01 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 157.0, 135.9, 131.5, 130.2, 127.6, 122.4, 106.0, 100.3, 98.3, 95.6, 51.5, 51.4, 46.6, 31.6, 25.0, 16.2, 8.7; IR (thin film) ν 3301, 2959, 2724, 2253, 1722, 1593, 1383; $[\alpha]_D$ = +6 (*c* 0.35, CH_2Cl_2); HRMS (E+) *m*/*z* 289.1795 $(M+H)^+$; calculated mass for $C_{18}H_{25}O_3^+$: 289.1798.

*(2R,3Z,7R,9E,11E)-12-(3,5-Dimethoxyphenyl)-1-((diphenylmethylene)amino)-2,7,10-trimethyldodeca-3,9,11-trien-5-one [(−)-**34**].* To a solution of alkyne (−)-**13** (1.6 g, 6.47 mmol) in THF (12 mL) at −78 °C was added dropwise LDA (2 M in THF, 3.2 mL, 6.4 mmol) and the resulting mixture was stirred at −78 °C for 1 h before warming to rt. After stirring for 1 h at rt, the reaction was cooled back to −78 °C and transferred via cannula to a solution of aldehyde (+)-**33** (940 g, 3.26 mmol) in THF (10 mL) at −78 °C. The resulting solution was stirred at −78 °C for 5 h, then warmed to rt, quenched with solid NH_4Cl, filtered, and concentrated *in vacuo*. Purification via flash chromatography (1% Et_3N in 15% EtOAc/hexane) afforded the intermediate alcohols (1.62 g, 3.02 mmol, 93%) as a yellow oil. The starting alkyne (−)-**13** was recovered in 46% yield: R_f = 0.27 (20% EtOAc/hexane).

The resulting diastereomeric mixture of alcohols was combined with NMO (1.06 mg, 9.04 mmol, 3 equiv) in CH_2Cl_2 (15 mL). To this solution at rt was added in portions over 30 min TPAP (266 mg, 0.76 mmol, 25 mol %) and the mixture was stirred at rt for 24 h. The resulting reaction was diluted with hexane (20 mL), filtered through a plug of silica gel eluting with 50% CH_2Cl_2/hexane, concentrated *in vacuo*, and further purified by flash chromatography (1% Et_3N in 15% Et_2O/hexane) to provide the corresponding alkynone (1.29 g, 2.42 mmol, 80%) as a pale yellow oil: R_f = 0.50 (20% EtOAc/hexane); ^1H NMR (400 MHz, C_6D_6) δ 7.89−7.83 (m, 2H), 7.15−7.03 (m, 6H), 6.94 (dd, *J* = 5.1, 3.1 Hz, 2H), 6.88 (d, *J* = 16.0 Hz, 1H), 6.78 (d, *J* = 1.7 Hz, 2H), 6.51 (dd, *J* = 11.8, 8.6 Hz, 2H), 5.44 (t, *J* = 7.5 Hz, 1H), 3.43 (dd, *J* = 13.7, 6.5 Hz, 1H), 3.37 (s, 6H), 3.32 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.93 (h, *J* = 6.8 Hz, 1H), 2.42 (dd, *J* = 14.8, 5.2 Hz, 1H), 2.35−2.19 (m, 2H), 2.04 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.89 (dt, *J* = 14.6, 7.3 Hz, 1H), 1.68 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 186.2, 168.6, 161.4, 140.2, 139.7, 136.7, 135.1, 134.4, 131.8, 130.0, 128.6, 128.5, 128.2, 127.97, 127.60, 126.4, 104.6, 99.7, 95.6, 82.0, 58.2, 54.5, 52.2, 35.1, 30.2, 28.4, 19.4, 17.7, 12.3; IR (thin film) ν 2931, 2209, 1669, 1592, 1381; $[\alpha]_D$ = +2 (*c* 0.68, CH_2Cl_2); HRMS (E+) *m*/*z* 534.3014 $(M+H)^+$; calculated mass for $C_{36}H_{40}NO_3^+$: 534.3003.

A mixture of the resulting alkynone (400 mg, 0.75 mmol), Lindlar catalyst (320 mg, 0.15 mmol Pd, 20 mol %), pyridine (0.9 mL, 11.25 mmol, 15 equiv), and toluene (6 mL) were stirred vigorously at rt

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under a H_2 atmosphere (balloon) for 24 h. The mixture was then filtered through Celite, concentrated *in vacuo*, and purified by flash chromatography (1% Et_3N in 8% EtOAc/hexane) to provide *cis*-enone (−)-**34** (245 mg, 0.45 mmol, 61%) as a pale yellow oil: R_f = 0.33 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, C_6D_6) δ 7.89−7.82 (m, 2H), 7.14−7.03 (m, 6H), 6.99−6.89 (m, 3H), 6.80 (d, J = 2.2 Hz, 2H), 6.53 (d, J = 16.0 Hz, 1H), 6.53 (t, J = 2.2 Hz, 1H), 6.00 (dd, J = 11.5, 9.5 Hz, 1H), 5.91 (d, J = 11.6 Hz, 1H), 5.54 (t, J = 7.4 Hz, 1H), 4.27−4.12 (m, 1H), 3.41 (d, J = 6.1 Hz, 2H), 3.37 (s, 6H), 2.31−1.90 (m, 5H), 1.75 (s, 3H), 1.17 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 200.0, 168.0, 161.8, 152.0, 140.6, 140.4, 137.5, 135.3, 134.8, 132.7, 130.1, 128.9, 128.7, 128.2, 127.94, 126.7, 126.6, 105.0, 100.1, 59.8, 54.9, 51.1, 35.7, 35.3, 30.4, 20.1, 18.6, 12.7; IR (thin film) ν 2957, 1688, 1592, 1380; $[\alpha]_D$ − 50.4 (*c* 0.47, CH_2Cl_2); HRMS (E+) *m*/*z* 536.3165 $(M+H)^+$; calculated mass for $C_{36}H_{42}NO_3^+$: 536.3160.

IMDA Cylization of (−)-34. To a solution of (*Z*)-enone (−)-**34** (65 mg, 121 μmol) in CH_2Cl_2 (2 mL) at 0 °C was added via syringe Me_2AlCl (0.9 M in heptane, 0.2 mL, 1.5 equiv) and the resulting yellow solution was stirred at 0 °C for 12 h. The reaction was then quenched with saturated aq $NaHCO_3$ (5 mL), extracted with Et_2O (3 × 10 mL), washed with brine (2 × 5 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide a yellow residue (43 mg, 80 μmol, 66%). ^{1}H NMR analysis of this crude reaction mixture showed a 2.6:2.6:16.1:1.0 of the four possible diastereomers (*exo*:*endo* 1.0:3.4). This residue was purified by flash chromatography (1% Et_3N in 8% EtOAc/hexane) to afford *endo*-chair product (+)-**35** (34 mg, 63 μmol, 52%) as a white solid.

*(3R,4aR,7S,8R,8aR)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((diphenylmethylene)amino)propan-2-yl)-3,5-dimethyl-2,3,4,4a,8,8a-hexahydronaphthalen-1(7H)-one [(+)-**35**].* White solid, R_f = 0.38 (10% EtOAc/hexanes); mp 138−145 °C; NMR data, including 2D NMR correlations, summarized in Table S8 in Supporting Information. IR (thin film) ν 3443, 2954, 2926, 1700, 1599; $[\alpha]_D$ + 149 (*c* 0.18, CH_2Cl_2); HRMS (E+) *m*/*z* 536.3163 $(M+H)^+$; calculated mass for $C_{36}H_{42}NO_3^+$: 536.3160.

Isomerization of (*Z*)-Enone (−)-34. To a solution of (*Z*)-enone (−)-**34** (55 mg, 103 μmol) in CH_2Cl_2 (1.5 mL) at −15 °C was added via syringe Me_2AlCl (0.9 M in heptane, 0.17 mL, 1.5 equiv) and the resulting yellow solution was stirred at −15 °C for 4 h. The reaction was quenched with saturated aq $NaHCO_3$ (3 mL), extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography to afford the corresponding (*E*)-enone *(2R,3E,7R,9E,11E)-12-(3,5-dimethoxyphen-yl)-1-((diphenylmethylene)-amino)-2,7,10-trimethyldodeca-3,9,11-trien-5-one* as the sole product (38 mg, 70 μmol, 68%): Colorless oil; R_f = 0.40 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz, C_6D_6) δ 7.88−7.82 (m, 2H), 7.14−7.04 (m, 6H), 6.97−6.88 (m, 4H), 6.78 (d, J = 2.2 Hz, 2H), 6.53 (d, J = 2.4 Hz, 1H), 6.50 (d, J = 11.0 Hz, 1H), 6.14 (dd, J = 16.0, 1.2 Hz, 1H), 5.54 (t, J = 7.5 Hz, 1H), 3.37 (s, 6H), 3.35−3.26 (m, 2H), 2.73−2.60 (m, 1H), 2.37 (dd, J = 15.4, 5.7 Hz, 1H), 2.28 (dq, J = 19.3, 6.3 Hz, 1H), 2.20−2.09 (m, 2H), 1.98 (dt, J = 14.5, 7.4 Hz, 1H), 1.75 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 198.3, 168.0, 161.4, 149.7, 140.2, 139.9, 137.1, 135.0, 134.4, 132.3, 129.9, 129.6, 128.5, 128.5, 128.09, 127.99, 127.8, 127.6, 126.4, 104.6, 99.7, 58.8, 54.5, 46.9, 38.3, 35.4, 30.1, 19.8, 17.2, 12.4; IR (thin film) ν 3439, 2958, 2929, 1665, 1622, 1592; $[\alpha]_D$ − 9.3 (*c* 0.45, CH_2Cl_2); HRMS (E+) *m*/*z* 536.3166 $(M+H)^+$; calculated mass for $C_{36}H_{42}NO_3^+$: 536.3160.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01677.

Author contributions, expansion of alkene region in crude ^{1}H NMR spectrum for IMDA cyclization of (−)-**34**, tabular NMR data, including 2D correlations, for compounds (−)-**16**, (−)-**17**, (−)-**19**, **27**, **28**, (+)-**29**, (+)-**30**, and (+)-**35**, and NMR spectra for new products (PDF)

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Notes

The authors declare no competing financial interest.

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(27) Attempts to convert the TMS group of **27** into a methyl group so as to access the neosymbioimine carbon skeleton currently have not met with success. Alternative strategies employing different bulky silyl groups that are more amenable to conversion to the methyl moiety are under consideration.

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