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High pi-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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J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.6b01677 • Publication Date (Web): 26 Aug 2016 Downloaded from http://pubs.acs.org on August 30, 2016

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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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TMS group exerts high exo-selectivity Exocyclic stereocenter induces high π -facial selectivity

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 world-wide 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 exoselective type I IMDA cyclization of dodeca-3,9,11-trien-5ones. 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 (+)-symbioimine³ and (+)-neosymbioimine⁴ from a symbiotic dinoflagellate Symbiodinium sp. colonizing a marine flatworm Amphiscolops sp. While no biological activity has been reported for its 7,10dimethylated congener, (+)-symbioimine is known to exhibit moderately selective COX-2 inhibition and promising antiosteoclastogenic 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 cycloaddition of (E)-enone 1 and imine cyclization or an endo-selective



IMDA reaction of dihydropyridinium 2 followed by epimerization at C-4 (Scheme 1). Snider⁵ and Thomson⁶ both employed the dihydropyridinium route in their respective syntheses of 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 im-ACS Paragon Plus Environment trienones such as 1 (R = H) undergo

Scheme 1. Proposed Biosyntheses of the Symbioimines

type I IMDA cycloadditions, they typically proceed via an *endo* transition state instead of the requisite *exo*-chair pathway.^{1a,9} Yamamoto demonstrated that bulky aluminium phenoxide Lewis acids can encourage *exo*-selective IMDA reactions of related (*E,E,E*)-trienenones.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).^{$2\bar{a}$} As expected, the cycloadditions all proceeded via an endo transition state. Dimethylaluminium chloride proved to be the best Lewis acid mediator. Use of Yamamoto's relatively less Lewis acidic bulky aluminium phenoxide reagents¹⁰ 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.

Scheme 2. Previous Studies.^{2a}



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 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 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.

Scheme 3. Two Potential Transition State Conformations¹⁸



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 (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 (*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

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



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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 acidmediated IMDA cyclization at various temperatures (Table 1). Similar to our previous studies,^{2a} only partial enone isomerization $(14\rightarrow 15)$ was observed at -78 °C (entry 1). Letting the reaction warm up to -30 °C over 12h 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 Supporting Infor*mation*).¹⁷ Determination of the absolute stereochemistry required conversion to the tricyclic imine 19 and comparison to known compounds (Table 5).^{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 BBr3-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 deter-

Table 1. IMDA Cyclization of Trienone (-)-14^a

Me₂AICI

CH₂Cl₂

temp

İMS



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тмs

^aReaction conditions: Me₂AlCl (1.2 equiv) in CH₂Cl₂ (0.03M). ^bIsolated yield after column chromatography for a single run. ^cDetermined by ¹H NMR analysis of the crude reaction product. ^dStarting (Z)-enone **14** recovered in 22%. ^e1.5 equiv Me₂AlCl used. Scheme 5. Synthesis of Tricyclic Imine (-)-19



mination 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 selectively converted into the corresponding gemdibromoalkene 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 (R)-(-)-Roche ester.

Scheme 6. Synthesis of IMDA Precursors 25 and 26



When 25 was treated with Me₂AlCl 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 BF₃ Et₂O was used as

the Lewis acid, the exo:endo ratio increased dramatically and there was a switch in diastereoselectivity now favoring exoproduct 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 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

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

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N=CPh₂

CPh₂

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υH

Me₂AlCl (1.5 equiv), CH₂Cl₂,

BF₃ Et₂O (1.5 equiv), CH₂Cl₂,

Мe

SiMe₃

Me₃S

conditions

-20 °C, 5h

-10 °C, 3.5h

conditions

N^{∞CPh}2

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SiMe₃

exo products

0

N^{, ∠CPh}2

2 Me

Ĥ.

SiMe

н

(+)-29 (2R)

endo product

27:28:29^a

1:2.4:2.7

2:1:0.3

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27 (2R)

N^{∞CPh}2

Å.

н

28 (2R)

2 Me

ŚiMe-

Yield (%)

 85^b

61^c

N^{∞CPh}2

2 .Me

ŚiMe₂

(-)-25 (2R)

[Ar = 3,5-(MeO)₂Ph]

entry

1

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tion mixture ^bCombined isolated yields of **27-29** after column chromatography for a single run. ^cCombined isolated yield of *exo* products **27** and **28** only.

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

^aDetermined by ¹H NMR spectroscopic analysis of the crude reac-



"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 Tl₂CO₃ 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 Pd₂(dba)₃ (3 mol %) and tri-2furylphosphine (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 LiAlH4-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 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.

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



In contrast to our observations with the Lewis acidmediated IMDA of TMS-trienones 14/15 (Table 1), 25 (Table 2) and 26 (Scheme 8), treatment of C-10 methylated 34 with Me₂AlCl provided a complex mixture of all four possible dia-

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stereomers, from which only the highly predominant *endo* product **35** could be isolated cleanly and in moderate yield (Scheme 10). 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.

Scheme 10. IMDA Cycloaddition of (-)-34



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 acidmediated IMDA cycloaddition of internally activated dodeca-3.9.11-trien-5-ones. Chirality centers in the connecting chain complicate the diastereoselectivity without cancelling 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, vet it can be removed readily with 0.5M TFA in THF. Overall, our efforts provide direct access to previously unavailable epimers of the symbioimine tricyclic imine framework requisite for on-going structure-activity relationship studies

EXPERIMENTAL SECTION

General Methods. All non-aqueous 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 3Å molecular sieves for at least 48h and sparged with dried and deoxygenated argon gas for at least 30 minutes.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 (HZrCp₂Cl). 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 60Å 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 two 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 degcm²g⁻¹ at 20 °C. All NMR spectra were taken on a 400 MHz or 500 MHz spectrometer at 300K, 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-5,7di-en-l-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 H₂O (6 mL). Argon was bubbled through the solution for 30 min, then KOH (0.4 g, 7.13 mmol, 1.36 equiv) and Pd(PPh₃)₄ (900 mg, 0.78 mmol, 15 mol %) were added. The resulting mixture was stirred at rt for 1h and then 50 $^{\circ}$ C for 3 h. After cooling to rt, the reaction was diluted with 50 mL EtOAc, then washed with brine, dried (MgSO₄), 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, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) v 3440, 2394, 1590, 1153; HRMS (E+) m/z 357.1851 (M+Na)⁺; calculated mass for C₁₉H₃₀NaO₃Si⁺: 357.1856.

(5Z,7E)-8-(3,5-Dimethoxyphenyl)-6-(trimethylsilyl)octa-5,7dienal (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 NaHCO₃ and extracted with Et₂O. The combined organic extract was washed with 5% aq LiCl, dried (MgSO₄), concentrated *in vacuo*, and purified by flash chromatography (20% Et₂O/hexane) to afford diene 8 (1.06 g, 3.19 mmol, 93%) as a pale yellow oil: $R_f = 0.38$ (20%) Et₂O/hexane); ¹H NMR (400 MHz, CDCl₃) 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 = 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); ¹³C NMR (100 MHz, CDCl₃) 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) v 2953, 2837, 2720, 1725, 1590; HRMS (E+) m/z 355.1691 (M+Na)⁺; calculated mass for C₁₉H₂₈NaO₃Si⁺: 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 (1.0M 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 NaHCO₃, extracted with Et₂O (4×150 mL), dried (MgSO₄), and purified by flash chromatography (20% Et₂O/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 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%) Et₂O/hexane): ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 140.9, 89.7, 66.3, 41.2, 15.5; $[\alpha]_{D} = -0.45$ (*c* 0.67, CHCl₃).

(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 (10mL, 71.7

mmol, 5.2 equiv), and DMAP (86 mg, 0.8 mmol, 5 mol %) in 20 mL CH₂Cl₂ 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 CH₂Cl₂. The reaction then was allowed to warm up to 25 °C and stirred at that temperature overnight. The resulting reaction mixture was diluted with Et₂O (100 mL), washed sequentially with saturated aq NaHCO₃ (2×50mL), H₂O (50 mL) and brine (50 mL), dried (Na₂SO₄), 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 Et₂O, washed sequentially with H₂O (3×50 mL) and brine (50 mL), dried (Na₂SO₄), 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 140.1, 90.5, 55.6, 38.7, 16.8; IR (thin film) v 2971, 2929, 2870, 2099, 1616, 1454, 1257; $[\alpha]_{D} = +1.25$ (c 0.56, CH₂Cl₂); HRMS (E+) m/z243.9126 $(M+3H-N_2)^+$; 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 PPh₃ (23 g, 87.75 mmol, 4 equiv). The resulting solution was heated to 50 °C and stirred for 3 d. H₂O (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/CH₂Cl₂) to provide amine (+)-12 (4.9 g, 20.8 mmol, 92%) as a brown oil: R_f = 0.28 (5% MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) $\delta 6.21$ (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); ¹³C NMR (100 MHz, CDCl₃) $\delta 142.3$, 89.1, 47.4, 42.2, 16.7; IR (thin film) ν 3376, 3290, 2963, 2926, 2666, 1611, 1456;:[α]_D = +7 (*c* 0.5, CH₂Cl₂); HRMS (E+) *m/z* 243.9122 (M+H)⁺; calculated mass for C₃H₁₀Br₂N⁺: 243.9154.

(R)-N-(Diphenylmethylene)-2-methylbut-3-yn-1-amine [(-)-13]. Amine (+)-12 (4.72 g, 19.43 mmol) was dissolved in dry CH₂Cl₂ 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 P₂O₅ for 2 d. The resulting ammonium chloride salt was slurried in 35 mL CH₂Cl₂ 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% Et₃N in 2% EtOAc/hexane) afforded the corresponding benzophenone imine (7.75 g, 19.03 mmol, 98%) in as a pale yellow oil: $R_f = 0.54$ (5% EtOAc/hexane); ¹H 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); ¹³C 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) v 3059, 2964, 2925, 1661, 1623, 1446, 1278; $[\alpha]_D = -39$ (*c* 0.28, CH₂Cl₂); 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 Et₂O at -78 °C was added LDA (2M 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 NH₄Cl. **NOTE**:

TLC never showed completion. The resulting mixture was filtered, concentrated *in vacuo*, and immediately purified by flash chromatography (1% Et₃N 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); ¹H 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); ¹³C 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, CH₂Cl₂); HRMS (E+) m/z 248.1426 (M+H)⁺; calculated mass for $C_{18}H_{18}N^+$: 248.1434.

The corresponding enantiomer, (*S*)-*N*-(*diphenylmethylene*)-2methylbut-3-yn-1-amine [(+)-**1**3], was made in an analogous manner starting from (*R*)-(–)-Roche ester: $[\alpha]_D = +10$ (*c* 0.18, CH₂Cl₂).

(R,3Z,9Z,11E)-12-(3,5-Dimethoxyphenyl)-1-((diphenylmethylene)amino)-2-methyl-10-(trimethylsilyl)dodeca-3,9,11-trien-5one [(-)-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 (2M 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 re-cooled 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 NH₄Cl. This resulting mixture was filtered, concentrated in vacuo, and purified by flash chromatography (1% Et₃N 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); ¹H 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); ¹³C NMR (100 MHz, C₆D₆) δ168.6, 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 CH₂Cl₂ 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% CH₂Cl₂/hexanes. The resulting filtrate was concentrated in vacuo and further purified by flash chromatography (1% Et₃N in 15% Et₂O/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); ¹H NMR (400 MHz, C₆D₆) 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– 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); ¹³C 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) v 2954, 2210, 1672, 1622, 1591, 1455; $[\alpha]_D = -6$ (*c* 0.4, CH₂Cl₂);

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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 H₂ 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% Et₃N 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); ¹H 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 = 7.4Hz, 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); ¹³C NMR (100 MHz, C₆D₆) 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) v 2955, 1690, 1592, 1381; $[\alpha]_{\rm D} = -69.5$ (c 0.2, CH₂Cl₂); 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 CH₂Cl₂ at the indicated temperature (Table 1) was added via syringe Me₂AlCl (0.9M 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 Na-HCO3 (5 mL), extracted with Et2O (3x10 mL), dried (MgSO4), and concentrated in vacuo. The resulting yellow residue was purified by flash chromatography (1% Et₃N in 10% EtOAc/hexane) to provide cycloaddition product (-)-16 as white solid plus varying amounts of the (E)-enone (-)-15. The diastereometric ratio for (-)-16 versus the corresponding *endo* adduct was determined by ¹H 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; ¹H NMR (400 MHz, C₆D₆) 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); ¹³C NMR (100 MHz, C₆D₆) 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) v 3442, 2956, 1591, 1381; $[\alpha]_D = -4.3$ (c 0.49, CH₂Cl₂); 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,8,8ahexahydronaphthal-en-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) v 3414, 2951, 1712, 1599, 1460, 1154; $[\alpha]_D = -81$ (c 0.53, CH₂Cl₂); HRMS (E+) m/z 580.3237 (M+H)⁺; calculated mass for C₃₇H₄₆NO₃Si⁺: 580.3242.

(4aS,7R,8S,8aR)-7-(3,5-dimethoxyphenyl)-8-((R)-1-((diphenylmethylene)amino)propan-2-yl)-2,3,4,4a,8,8ahexahydronaphtha*len-1(7H)-one [(-)-17]*. To a solution of (-)-16 (50 mg, 86 µmol) and 5 mL CH₃CN at rt in a Nalgene[®] screw-cap plastic bottle was added 50% aqueous HBF₄ (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 Na-HCO₃ (15 mL) and stirred for 20 min before extracting with EtOAc (3×15 mL) and drying (MgSO₄). The resulting product was purified by flash chromatography (1% Et₃N in 10% EtOAc/hexane) to provide alkene (-)-17 (39 mg, 77 µmol, 89%) as a white solid: $R_f = 0.37$ (1% Et₃N 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) v 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 0.5M aq TFA (2 mL). The reaction was warmed to 50 \mathbb{C} and stirred at that temperature for 4 h. After cooling to rt, the reaction was then quenched with saturated aq NaHCO₃ (20 mL) and stirred for 30 min before extracting with EtOAc (3×20mL) and drying (MgSO₄). The resulting product was purified by flash chromatography (1% Et₃N/EtOAc) to provide imine (-)-18 (60 mg, 184 μ mol, 95%) as a yellow oil: $R_f = 0.38$ (10%) MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) v 3435, 2927, 1656, 1605, 1594, 1459; $[\alpha]_{D} =$ -221 (c 0.43, CH₂Cl₂); HRMS (E+) m/z 326.2109 (M+H)⁺; calculated mass for C₂₁H₂₈NO₂⁺: 326.2115.

5-((3*R*,3*aI*,3*4*5,6*aR*)-3-methyl-3,3*a*,3*a*1,4,6*a*,7,8,9-octahydro-2*H*-benzo[*de*]quinolin-4-yl)benzene-1,3-diol [(-)-19]. To a solution of (-)-18 (29.5 mg, 91 µmol) in 8 mL CH₂Cl₂ at 0 °C was added BBr₃ (1M in CH₂Cl₂, 0.45 mL, 5 equiv). After stirring at 0 °C for 2.5 h, the reaction was quenched with saturated aq NaHCO₃ (10 mL), extracted with 3% MeOH/EtOAc (3×10mL), dried (Na₂SO₄), and purified by gradient flash chromatography (10% MeOH/CHCl₃→15% MeOH/CHCl₃) to provided bisphenol (-)-19 (26.5 mg, 89 µmol, 98%) as a white solid: R_f = 0.43 (15% MeOH/CHCl₃); mp >280 °C; NMR data, including 2D NMR correlations, are summarized in Table S3 in *Supporting Infor*mation; IR (thin film) v3444, 1637; [α]_D = -108 (*c* 0.012, CHCl₃); HRMS (E+) *m*/2 298.1807 (M+H)⁺; calculated mass for C₁₉H₂₄NO₂⁺: 298.1802.

(*R*)-*Propyl* 6,6-*dibromo-3-methylhex-5-enoate* [(+)-**21**]. To a solution of (*R*)-3-methyl-5-oxo-5-propoxypentanoic acid¹⁹ (92 %ee, 7.6 g, 40 mmol) in THF (133 mL) at 0 °C was added via syringe BH₃•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 H₂O (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 SiO₂ 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: ¹H NMR (500 MHz, CDCl₃) 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•H₂O (7.03 g, 60 mmol, 1.5 equiv), and crushed 4Å molecular sieves (~10 g) in CH₂Cl₂ (250 mL) and MeCN (10 mL) at rt was added TPAP (350 mg, 2.5 mol %) 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 SiO₂ eluting with Et₂O (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); ¹H NMR (500 MHz, CDCl₃) 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 CH₂Cl₂ (400mL) and cooled to -20 °C before adding PPh₃ (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% Et₂O/hexane) showed completion. The mixture was then diluted with hexane (400 mL), filtered through a plug of SiO₂ 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% Et₂O/Hex); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) & 172.6, 136.5, 90.0, 66.0, 40.9, 39.6, 29.7, 21.9, 19.6, 10.4; IR (thin film) v 2964, 2877, 1732, 1619; $[\alpha]_D = +9.2$ (c 1.0, CHCl₃); 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 CH₂Cl₂ at -15 °C was added DIBAL (1M in hexane, 12 mL, 2.56 mmol) and the resulting reaction mixture was allowed to warm to 25 $\,$ $\,$ $\,$ $\,$ $\,$ $\,$ $\,$ $\,$ $\,$ over 5 h. The reaction was then guenched with 1M ag Rochelle's salt (30 mL) and stirred for 30 min before extracting with Et₂O $(3 \times 50 \text{mL})$, drying (MgSO₄), 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 137.4, 89.5, 60.9, 40.3, 39.2, 29.3, 19.6; IR (thin film) v 3335, 2957, 2927, 1457; $[\alpha]_{\rm D}$ +3 (c 0.4, CH₂Cl₂).

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 (1.6M 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, Me₃SiCl (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 Et₂O (3x50 mL). The organic extracts were washed with brine, dried (MgSO₄), 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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; [α]_D +7 (*c* 0.3, CH₂Cl₂); HRMS (E+) *m*/*z* 185.1364 (M+H)⁺; calculated mass for C₁₀H₂₁OSi⁺: 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 (1M in hexane, 10 mL, 2.6 equiv). The resulting solution was heated to reflux (70 ^oC) and stirred at that temperature for 24 h. The solution was then cooled to -78 °C, after which a solution of I₂ (4 g, 15.76 mmol, 4 equiv) in Et₂O (60 mL) was added dropwise by addition funnel. After stirring at -78 °C for 2 h, the reaction was carefully quenched by pouring into 1M HCl (30 mL). The maroon organic layer was separated, and the aqueous layer was extracted with Et₂O (3×100 mL). The combined organic layers were washed sequentially with saturated aq Na₂S₂O₃ and brine, dried (MgSO₄), 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); ¹H NMR (400 MHz, CDCl₃) 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 = 6.6Hz, 3H), 0.26 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.2, 107.8, 61.0, 42.3, 39.4, 29.9, 19.5, 1.4; IR (thin film) v 3349, 2957, 2927, 1250, 844; [a]_D +3.3 (c 0.36; CH₂Cl₂); HRMS (E+) m/z 335.0288 (M+Na)⁺; calculated mass for C₁₀H₂₁IONaSi⁺: 335.0299.

(R,5Z,7E)-8-(3,5-Dimethoxyphenyl)-3-methyl-6-(trimethylsilyl)octa-5,7-dien-1-ol [(+)-24]. Vinyl iodide (+)-23 (770mg, 2.47 mmol) and pinacol boronate 6 (1.07 g, 3.69 mmol, 1.5 equiv) were combined in THF (10 mL) and deionized H₂O (2.5 mL). Argon was bubbled through the solution for 30 min, then KOH (208 mg, 3.7 mmol, 1.5 equiv) and Pd(PPh₃)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 (MgSO₄), 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) v 3381, 2955, 1592, 1459; $[\alpha]_D$ +1.2 (c 0.33, CH₂Cl₂); HRMS (E+) m/z $349.2200 (M+H)^+$; calculated mass for C₂₀H₃₃O₃Si⁺: 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 NaHCO₃/H₂O and extracted with Et₂O. The combined organic extract was washed with 5% aq LiCl, dried (MgSO₄), concentrated *in vacuo*, and purified by flash chromatography (15% Et₂O/hexane) to give aldehyde (+)-**24** (410 mg, 1.18 mmol, 87%) as a pale yellow oil: R_f = 0.53 (10% EtOAc/hexane); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100

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MHz, CDCl₃) 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; [α]_D +5.9 (c 0.27, CH₂Cl₂); HRMS (E+) m/z 369.1850 (M+Na)⁺; calculated mass for C₂₀H₃₀NaO₃Si⁺: 369.1857.

(2R, 3Z, 7R, 9Z, 11E)-12-(3, 5-Dimethoxyphenyl)-1-((diphenylmethylene)amino)-2,7-dimethyl-10-(trimethylsilyl)dodeca-3,9,11trien-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 (2M 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 NH₄Cl, filtered, concentrated, and purified via flash chromatography (1% Et₃N 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: ¹H NMR (400 MHz, C₆D₆) & 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 (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); ¹³C NMR (100 MHz, C₆D₆) 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 CH₂Cl₂ (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% CH₂Cl₂/hexane. The solution was concentrated and further purified by flash chromatography (1% Et₃N 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); ¹H 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); ¹³C 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) v 2957, 2211, 1670, 1622, 1592; $[\alpha]_D$ –1.5 (c 0.2, CH₂Cl₂); HRMS (E+) m/z592.3244 (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 H₂ atmosphere (balloon) for 24 h. The mixture was then filtered through Celite, concentrated *in vacuo*, and purified by flash chromatography (1% Et₃N 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); ¹H NMR (400 MHz, C₆D₆) 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); ¹³C NMR (100 MHz, C₆D₆) 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) v 3438, 2957, 1689, 1592; $[\alpha]_D$ –54 (c 0.41, CH₂Cl₂); HRMS (E+) m/z 594.3396.

(2S,3Z,7R,9Z,11E)-12-(3,5-Dimethoxyphenyl)-1-((diphenylmethylene)amino)-2,7-dimethyl-10-(trimethylsilyl)dodeca-3,9,11trien-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 (2M 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, 2.37mmol) 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 NH₄Cl, filtered, concentrated, and purified via flash chromatography (1% Et₃N 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 CH₂Cl₂ (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% CH₂Cl₂/hexane. The solution was concentrated and further purified by flash chromatography (1% Et₃N 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 H₂ atmosphere (balloon) for 17 h. The mixture was then filtered through Celite, concentrated in vacuo, and purified by flash chromatography (1% Et₃N 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); ¹H NMR (400 MHz, C₆D₆) 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); ¹³C 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) v 3374, 2928, 1688, 1577.9, 1453, 1407; [α]_D +74.5 (*c* 0.11, CH₂Cl₂); HRMS (E+) m/z 594.3411 (M+H)⁺; calculated mass for C₃₈H₄₈NO₃Si⁺: 594.3398.

IMDA Cyclization of (–)-**25.** To a solution of (*Z*)-enone (–)-**25** (35 mg, 59 µmol) in CH₂Cl₂ (2.5 mL) at –20 °C was added via syringe Me₂AlCl (0.9M 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 NaHCO₃ (5 mL), extracted with Et₂O (3x10 mL), dried (MgSO₄), and concentrated *in vacuo*. Crude ¹H 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% Et₃N in 8% EtOAc/hexane) afforded the *exo* products **27** and **28** in a 1:3 ratio, as determined by ¹H NMR analysis (21 mg, 35.4 µmol, 60%) and (+)-**29** (9 mg, 26%). **Note:** Using Lewis acid BF₃ Et₂O 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 ¹H and ¹³C NMR spectra. 2D-NMR analysis was conducted on a roughly 1:1 mixture of **27:28** to determine the absolute stere-ochemistry of each diastereomer.

(3R,4aS,7R,8R,8aR)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((di-phenylmethylene)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) v 3443, 2955, 1711, 1599; HRMS (E+) m/z 594.3393 (M+H)⁺; calculated mass for C₃₈H₄₈NO₃SI⁺: 594.3398.

(3R,4aR,7S,8S,8aS)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((di-phenylmethylene)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 C₃₈H₄₈NO₃SI⁺: 594.3398.

(3R,4aR,7S,8R,8aR)-7-(3,5-Dimethoxyphenyl)-8-((R)-1-((di-phenylmethylene)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; [α]_D +148 (c 0.15, CH₂Cl₂); HRMS (E+) m/z 594.3393 (M+H)⁺; calculated mass for C₃₈H₄₈NO₃SI⁺: 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 CH₂Cl₂ (3 mL) at -20 ℃ was added via syringe Me₂AlCl (0.9M in heptane, 0.18 mL, 2 equiv) and the resulting yellow solution was stirred at $-20 \ \mathrm{C}$ for 4 h. The reaction was then quenched with saturated aq NaHCO₃ (5 mL), extracted with Et₂O (3x10 mL), dried (MgSO₄), concentrated in vacuo, and purified by flash chromatography (1% Et₃N 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) v 3446, 2954, 1711, 1600, 1458, 1154; $[\alpha]_{D}$ +158.7 (c 0.046,CH₂Cl₂); HRMS (E+) m/z594.3412 (M+H)⁺; calculated mass for $C_{38}H_{48}NO_3SI^+$: 594.3398.

(*R*,5*Z*,7*E*)-*Propyl* 6-bromo-8-(3,5-dimethylphenyl)-3-methylocta-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 Tl₂CO₃ (17.1 g, 36.6 mmol, 2.0 equiv) in 4:1 THF/H₂O (180 mL) was degassed by bubbling N₂ through the mixture for 20 min before adding Pd(PPh₃)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 H₂O (150 mL) and extracting with EtOAc (3x100 mL). The combined organics were dried (MgSO₄), concentrated, and purified by gradient flash chromatography $(5 \rightarrow 15\% \text{ EtOAc/hexane})$ 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), Cs₂CO₃ (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/H₂O (25 mL) was degassed by bubbling argon through the mixture for 30 min before adding Pd₂(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 (3x50 mL), dried (MgSO₄), concentrated in vacuo, and purified by flash chromatography (5% EtOAc/hexane) to provide diene (+)-31 (1.75 g, 66%) as a yellow oil: $R_f = 0.47 (10\% \text{ EtOAc/hexane}); {}^{1}\text{H}$ NMR (500 MHz, CDCl₃) 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 $(d, J = 6.3 \text{ Hz}, 3\text{H}), 0.94 (t, J = 7.4 \text{ Hz}, 3\text{H}); {}^{13}\text{C} \text{ NMR} (125 \text{ MHz}, 3\text{H})$ CDCl₃) & 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) v 2962, 2837, 1730, 1590, 1457, 1204, 1154; $[\alpha]_{\rm D} = +6.5$ (c 0.90, CHCl₃); HRMS (E+) *m/z* 433.0995 & 435.0964 (M+Na)⁺; calculated mass for $C_{20}H_{27}BrNaO_4^+$: 433.0985 & 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-Bu)₃]₂ (75 mg, 0.24 mmol, 2.0 mol %) in THF (80 mL) at 0 °C was added slowly via syringe Me₂Zn (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 NH₄Cl (50 mL) and extracted with EtOAc (3x50 mL). The combined organics were dried (MgSO₄) 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, CDCl₃) δ 6.79 (d, J = 16.0 Hz, 1H), 6.57 (d, J = 2.3 Hz, 2H), 6.40 (d, J = 16.0Hz, 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); ¹³C NMR (125 MHz, CDCl₃) 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) v 2962, 2837, 1731, 1590, 1456, 1424, 1328, 1204, 1153, 1063; $[\alpha]_{D} = +4.0$ (*c* 0.90, CHCl₃).

To a solution of crude ester (4.7 g, ~12.2 mmol) in Et₂O (95 mL) at 0 °C was added in one portion LiAlH₄ (0.51 g, 13.4 mmol, 1.1 equiv). After 1 h at 0 °C, 1M aq Rochelle's salt (100 mL) was added slowly and the mixture stirred for 1 h before extracting with EtOAc (3x50 mL), drying (MgSO₄) 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, CDCl₃) 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, 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); ¹³C NMR (125 MHz, CDCl₃) 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) v 3356, 2930, 2836, 1589, 1457, 1424, 1203, 1152, 1062; $[\alpha]_{D} = +3.4$ (c 1.0, CHCl₃); HRMS (E+) m/z 313.1746 (M+Na)⁺; calculated mass for C₁₈H₂₆NaO₃⁺: 313.1775.

(*R*,5*E*,7*E*)-8-(3,5-Dimethoxyphenyl)-3,6-dimethylocta-5,7-dienal [(+)-33]. To a solution of alcohol (+)-32 (840 mg, 2.89

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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 Na-HCO₃/H₂O and extracted with Et₂O. The combined organic extract was washed with 5% aq LiCl, dried (MgSO₄), concentrated in vacuo, and purified by flash chromatography (25% Et₂O/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, CDCl₃) 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, 3.10 Hz)J = 12.9 Hz, 1H), 2.32–2.14 (m, 4H), 1.85 (s, 3H), 1.01 (d, J = 5.8Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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) v 3301, 2959, 2724, 2253, 1722, 1593, 1383; $[\alpha]_D = +6$ (c 0.35, CH₂Cl₂); HRMS (E+) m/z 289.1795 (M+H)⁺; calculated mass for C₁₈H₂₅O₃⁺: 289.1798.

(2*R*,3*Z*,7*R*,9*E*,11*E*)-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 (2M 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 NH₄Cl, filtered, and concentrated *in vacuo*. Purification via flash chromatography (1% Et₃N 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 CH₂Cl₂ (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% CH₂Cl₂/hexane, concentrated in vacuo, and further purified by flash chromatography (1% Et₃N in 15% Et₂O/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); ¹³C 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) v 2931, 2209, 1669, 1592, 1381; $[\alpha]_D = +2$ (c 0.68, CH₂Cl₂); HRMS (E+) m/z 534.3014 (M+H)⁺; calculated mass for C₃₆H₄₀NO₃⁺: 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 under a H₂ atmosphere (balloon) for 24 h. The mixture was then filtered through Celite, concentrated *in vacuo*, and purified by flash chromatography (1% Et₃N 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); ¹H NMR (400 MHz, C₆D₆) 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); ¹³C NMR (100 MHz, C₆D₆) & 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) v 2957, 1688, 1592, 1380; $[\alpha]_D$ –50.4 (c 0.47, CH₂Cl₂); HRMS (E+) m/z 536.3165 (M+H)⁺; calculated mass for C₃₆H₄₂NO₃⁺: 536.3160.

IMDA Cylization of (–)-**34.** To a solution of (*Z*)-enone (–)-**34** (65 mg, 121 µmol) in CH₂Cl₂ (2 mL) at 0 °C was added via syringe Me₂AlCl (0.9M 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 NaHCO₃ (5 mL), extracted with Et₂O (3x10 mL), washed with brine (2x5 mL), dried (MgSO₄), and concentrated *in vacuo* to provide a yellow residue (43 mg, 80 µmol, 66%). ¹H 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% Et₃N 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-((di-phenylmethylene)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) v 3443, 2954, 2926, 1700, 1599; [α]_D +149 (c 0.18, CH₂Cl₂); HRMS (E+) m/z 536.3163 (M+H)⁺; calculated mass for C₃₆H₄₂NO₃⁺: 536.3160.

Isomerization of (Z)-Enone (-)-34. To a solution of (Z)enone (-)-34 (55 mg, 103 µmol) in CH₂Cl₂ (1.5 mL) at -15 °C was added via syringe Me₂AlCl (0.9M 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 NaHCO₃ (3 mL), extracted with CH₂Cl₂, dried (MgSO₄), concentrated in vacuo, and purified by flash chromatography to afford the corresponding (E)-enone (2R,3E,7R,9E,11E)-12-(3,5-dimethoxyphenyl)-1-((diphenylmethylene)amino)-2,7,10-trimethyldodeca-3,9,11trien-5-one as the sole product (38 mg, 70 µmol, 68%): Colorless oil; $R_f = 0.40$ (15% EtOAc/hexanes); ¹H NMR (400 MHz, C_6D_6) δ7.88–7.82 (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, 1000 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); ¹³C NMR (100 MHz, C₆D₆) 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) v 3439, 2958, 2929, 1665, 1622, 1592; $[\alpha]_D$ -9.3 (c 0.45, CH₂Cl₂); HRMS (E+) m/z 536.3166 (M+H)⁺; calculated mass for $C_{36}H_{42}NO_3^+$: 536.3160.

ASSOCIATED CONTENT

Supporting Information

Author contributions, expansion of alkene region in crude ¹H NMR spectrum for IMDA cyclization of (-)-**34**, tabular NMR data, including 2D correlateions, for compounds (-)-**16**, (-)-**17**, (-)-**19**, **27**, **28**, (+)-**29**, (+)-**30**, and (+)-**35**, and NMR spectra for new products (PDF). This material is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support provided by the NSFC (Nos. 21372159, J1310008 & J1103315) and the University of Virginia (UVA) Institute on Aging. We thank Prof. J. A. Marshall (UVA) for generously providing multi-gram quantities of *O*-TBDPS-protected (*S*)-(+)-Roche ester. J.P.B. was supported by a Presidential Fellowship from the UVA Graduate School of Arts & Sciences. Compound characterization (NMR, HRMS, IR) was performed by the Comprehensive Specialized Laboratory Training Platform, College of Chemistry, Sichuan University.

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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.