

Transition Metal-Catalyzed Intramolecular [4 + 2] Cycloadditions: Mechanistic and Synthetic Investigations

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Abstract: The nickel-catalyzed intramolecular cycloaddition of dienes with unactivatable alkynes is found to proceed under mild conditions while the corresponding Diels-Alder cycloaddition of the same substrates either fails or occurs only under forcing conditions. The nickel-catalyzed cycloaddition is also shown to occur with retention of stereochemistry and is not significantly influenced by electronic effects. Finally, the catalyzed process is shown to be applicable to the synthesis of angularly substituted bicycles, including the CD ring systems of steroids and vitamin D. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Introduction

Cycloaddition reactions serve as exceptionally useful strategy level processes for the construction of complex molecules.¹ Their utility arises in part from their capacity to produce a new ring with up to four new stereogenic centers in a single operation that is often practical, simple, and environmentally acceptable. There are numerous situations, however, in which the use of these reactions is limited for operational reasons or precluded on theoretical grounds. Examples of the former include cases in which the otherwise highly useful Diels-Alder [4 + 2] cycloaddition does not occur or works only under forcing conditions due to mismatched HOMO-LUMO interactions. The latter situation is encountered in a variety of cycloaddition reactions such as the [4 + 4] cycloadditions of dienes which are forbidden in the ground state and are often entropically disfavored in the excited state.²

Since the 1980's, our group has been exploring the use of transition metal catalysis as a means to circumvent the operational or theoretical restrictions associated with several classes of cycloadditions, generically of the [m + n] component variety (m,n = 1,2,3,4,5,...).^{3,4} These studies have resulted thus far in the first examples and synthetic applications of the transition metal-catalyzed intramolecular [4 + 4] cycloaddition of dienes,^{3c–g} a process which has taken the pioneering contributions of Reed, Wilke, and others⁵ on simple diene cycloadditions into the challenging arena of complex molecule synthesis. We have also described the first studies on metal-catalyzed intramolecular [4 + 2] cycloadditions.^{3h–i,6} More recently, we have reported the first examples of a new cycloaddition reaction, involving the metal-catalyzed [5 + 2] cycloaddition of alkynes and vinylcyclopropanes.^{3j}

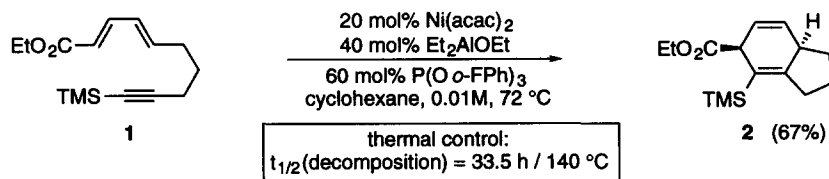
We describe herein results arising from our continuing studies on the transition metal-catalyzed intramolecular [4 + 2] cycloaddition between dienes and π -systems.⁷ Offering several advantages over the Diels-Alder cycloaddition,⁸ these metal-catalyzed cycloadditions proceed through a distinct multistep mechanism and are thus exempt from the often restrictive electronic requirements that govern the concerted Diels-Alder process. Alkenes and alkynes lacking a flanking carbonyl group, for example, which are often poor dienophiles in the Diels-Alder reaction, exhibit excellent reactivity in the metal-catalyzed cycloaddition.

Several representative examples have now been reported for which the Diels–Alder cycloaddition fails, or proceeds only slowly, even at elevated temperatures, while the metal-catalyzed cycloaddition occurs efficiently and rapidly, often at room temperature.^{3h} Moreover, in contrast to the Diels–Alder reaction, in which chemo- and stereoselectivity are dictated principally by the diene and dienophile substrates, the selectivity of the metal-catalyzed cycloaddition can be controlled and even reversed by the catalyst.³ⁱ As part of our continuing studies on the scope and limitations of this novel class of reactions, we describe herein the first study of the effects of starting material electronic perturbations upon the rate and efficiency of the nickel(0)-catalyzed intramolecular cycloaddition of dienyne. These cycloadditions were found to be tolerant of modifications in the electronic properties of the diene components. The stereochemical relationship between the geometry of the starting diene and the stereochemistry of the cycloadduct has also been determined. Developed in the context of a strategy for the synthesis of steroids and vitamin D analogs, this study also furnishes the first solution to a problem previously encountered in attempts to apply this metal-catalyzed cycloaddition to the synthesis of bicyclic systems bearing an angular methyl group, a prominent feature of numerous natural and non-natural polycycles.⁹

Electronic Effects

Transition metal catalysts have been shown to effect the intramolecular [4 + 2] cycloadditions of unactivatable dienyne under conditions substantially milder than those required for the corresponding thermal Diels–Alder reactions.^{3h–i} In many other cases, the transition metal-catalyzed process represents the *only* method for achieving the desired transformation. Examples of this situation include substrates which are unreactive or which contain functionality too unstable to withstand the thermal conditions required to effect cycloaddition, undergoing a more facile competing process or decomposition. Notwithstanding these advantages and the sensitivity of the Diels–Alder reaction to electronic perturbations,⁸ electronic effects in transition metal-catalyzed intramolecular [4 + 2] cycloadditions have not been investigated.

Dienyne substrate **1** was prepared as an initial test of the comparative role of electronic effects on the course of the concerted and metal catalyzed [4 + 2] cycloaddition (Scheme 1). Coupling of 6-trimethylsilyl-5-hexyn-1-ol¹⁰ with commercially available triethyl 4-phosphono-crotonate in a Wadsworth–Horner–Emmons olefination¹¹ gave the desired *E,E*-dienyne-ester **1**. The electron withdrawing nature of the ethyl ester positioned at the terminus of the diene makes this dienyne a poor candidate for the Diels–Alder reaction.⁸ Illustrative of this point, when **1** was heated in a resealable NMR tube with an internal standard, no reaction was observed up to a threshold temperature of 140 °C, at which point the dienyne began to decompose with no indication of [4 + 2] cycloadduct formation. The half-life of dienyne decomposition was measured to be 33.5 h at 140 °C. *In short, dienyne 1 does not undergo a conventional Diels–Alder reaction even under forcing conditions.*

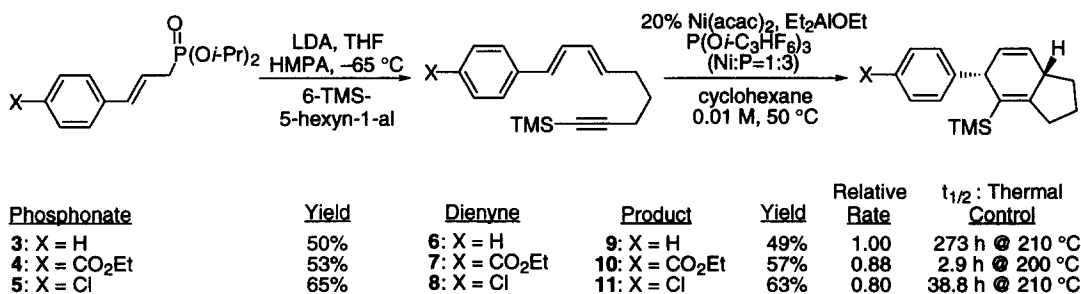


Scheme 1

The nickel(0)-catalyzed intramolecular [4 + 2] cycloaddition of dienyne **1** was investigated next. Exposure of this substrate to the conditions given in Scheme 1 led to the formation of cycloadduct **2** in 67% yield. *Thus, while the thermal Diels–Alder cycloaddition of 1 fails, the metal catalyzed reaction provides the cycloadduct 2 in reasonable yield under relatively mild conditions.* Additional studies on this substrate revealed that it is less reactive under conditions previously used in other catalyzed cycloadditions (10% Ni(COD)₂, 30% P(Oo-BiPh)₃, THF).^{3h} A variety of ligands having a wide range of steric and electronic values

were also examined. While the efficiency of the cycloaddition of **1** did not improve, higher conversions were obtained with increasing χ value of the ligand (greater electron withdrawing ability).¹² Non-polar solvents such as cyclohexane and toluene were found generally to increase reaction rates over those run in THF. The ability of THF to act as a coordinating ligand to nickel and inhibit substrate coordination is a plausible explanation for this phenomenon. Finally, while the nickel(0) sources, $\text{Ni}(\text{COD})_2$ and $\text{Ni}(\text{acac})_2/\text{Et}_2\text{AlOEt}$, are generally interchangeable,¹³ the $\text{Ni}(\text{acac})_2$ system gave slightly higher yields for this particular transformation and was less susceptible to catalyst decomposition. These reactivity differences could be due to interaction of the aluminum salts generated in these reactions with the ester functionality of the substrate.¹⁴

To further probe the relationship between dienyne electronic perturbation and reactivity toward the nickel-catalyzed intramolecular [4 + 2] cycloaddition, a series of *para*-substituted aryl dienynes was prepared (Scheme 2). This conventional approach to decoupling steric and electronic perturbations allowed for a study of electronic effects imparted by variations of a *para* substituent on an aromatic ring coupled to the diene without changing the steric environment around the diene.¹⁵ The *E,E*-dienynes **6–8** were prepared for this study by the same olefination procedure used for the previous substrate. The requisite allylic phosphonates were assembled by three different methods. Arbuzov reaction¹⁶ of cinnamyl chloride with isopropyl phosphite gave the unsubstituted phosphonate **3**. The ethyl ester phosphonate **4** was prepared by a Heck arylation¹⁷ of diisopropyl allylphosphonate using *p*-bromo ethyl benzoate. The *p*-chloro phosphonate **5** was prepared from the corresponding commercially available substituted cinnamic acid by NaBH_4 reduction of the mixed anhydride to give the allylic alcohol,¹⁸ followed by iodide formation¹⁹ and Arbuzov reaction.²⁰



Scheme 2

The nickel(0)-catalyzed intramolecular [4 + 2] cycloadditions of these *p*-aryl-substituted dienyne substrates (**6–8**) were then investigated. Conditions were determined for the efficient cyclization of dienyne **7** and were then applied to the remaining substrates. These conditions were found to be 20% $\text{Ni}(\text{acac})_2$, 40% Et_2AlOEt , 60% $\text{P}(\text{O}i\text{-C}_3\text{HF}_6)_3$ in cyclohexane at 50 °C, which gave a 57% yield of cyclized product **10**. The highly electron-withdrawing tris(hexafluoroisopropyl)phosphite ($\chi = 51.3$) was found to enhance catalyst reactivity considerably and became the standard ligand for these cycloadditions. As an added benefit, the volatility of this ligand removes the need for difficult chromatographic separations of otherwise tenacious phosphite reagents. To ensure purity, however, this ligand must be prepared from the hexafluoroisopropoxide salt and PCl_3 according to the method of Yamamoto.²¹ The other substrates (**6** and **8**) were then subjected to the cycloaddition conditions used for **7**. Isolated yields of 49% and 63% were obtained, respectively, and were not optimized with respect to these systems for comparison purposes.²²

In order to compare the Diels–Alder reactivities of these dienynes, thermal controls were performed in resealable NMR tubes using cyclohexane- d_{12} solvent and 1,3,5-trimethoxybenzene as an internal standard. The hydrogen-substituted dienyne **6** was the only one of these substrates which actually cyclized to give the normal Diels–Alder product. This reaction, however, was extremely slow, having a half-life of 273 h at 210 °C. The efficiency of flash vacuum thermolysis was not investigated for any of these Diels–Alder reactions. The ethyl ester- and chloro-substituted dienynes **7** and **8** were consumed somewhat more rapidly,

but gave cyclized products apparently lacking a vinyltrimethylsilyl group. Trace acid contamination could be responsible for silane removal in the starting materials or products under these harsh thermal conditions.²³ *Thus, while these substrates either fail to undergo the Diels-Alder reaction or react only under forcing conditions, they are smoothly converted to their [4 + 2] cycloaddition products, in good yields, in the presence of nickel catalysts.*

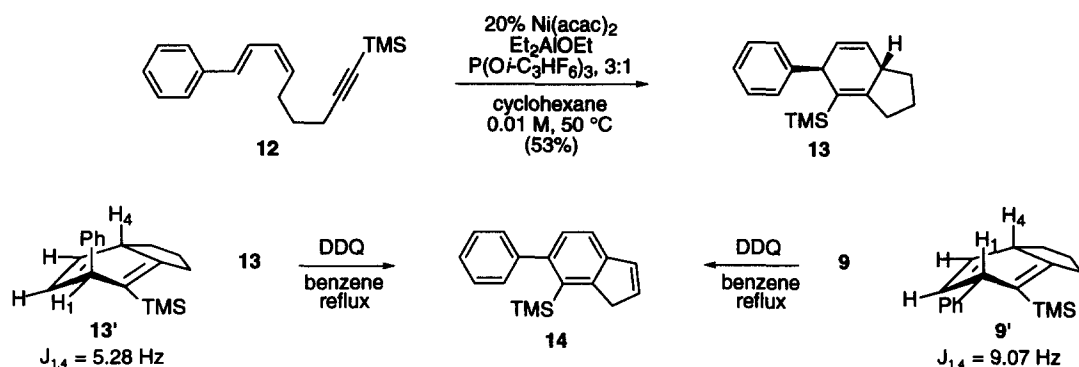
In order to quantify the effect of substrate electronic perturbations upon the rates of the nickel-catalyzed cycloadditions, a relative rate study was performed in which two different dienyne were cyclized competitively in the same reaction vessel. This method alleviated reproducibility problems in that both substrates were assured access to identical catalyst concentrations. Each of the substituted dienyne **7** and **8** ($X = \text{CO}_2\text{Et}$, Cl) were individually cyclized in competition with the unsubstituted substrate **6** ($X = \text{H}$). The relative cycloaddition rates were calculated by quenching aliquots at various reaction times and comparing the disappearance of dienyne starting materials relative to the triphenylene internal standard by HPLC. The relative rates, kX/kH , were determined to be 0.88 and 0.80 respectively.²⁴

Finally, correlation of these relative rates with the electronic properties of the dienyne substituent groups was attempted. Interestingly, application of the standard σ_p constants to the relative rates gave a non-linear relationship. The use of other constants such as σ_p^+ , σ_p^- , and \mathcal{R} gave similar results. The relationship between reaction rate and substrate electronic properties for the nickel-catalyzed [4 + 2] cycloaddition is thus not simple. This is not surprising given the multistep nature of these reactions and the possibility that rate determining steps could change from one catalyst system to another. Nevertheless, it is clear that the nickel(0)-catalyzed intramolecular [4 + 2] cycloaddition is relatively insensitive to the electronic properties of the dienyne substrates, a finding which has great synthetic value. Over the range of electronic perturbations examined, the reactions rates differed by less than a factor of two. In addition, the catalyst has been shown to tolerate an ester functionality in the organic substrates without difficulty, thus expanding the versatility of this cycloaddition for synthetic applications. The nickel-catalyzed [4 + 2] cycloaddition represents a mild and efficient alternative to the nonactivated Diels-Alder reaction in cases which, for electronic reasons, the latter reaction proceeds very slowly or fails altogether.

Diene Geometry

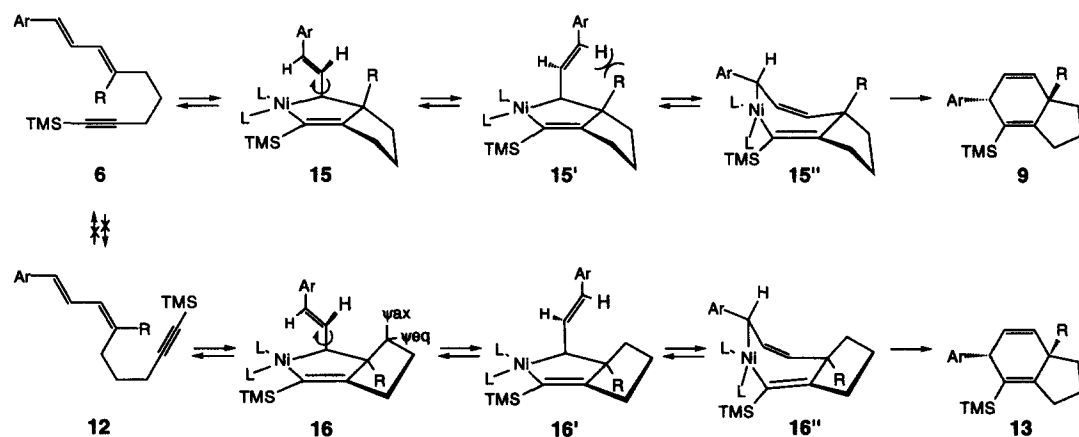
Conservation of Diene Stereochemistry. The ability of the Diels-Alder reaction to create up to four new stereocenters on a cyclohexene ring in a highly predictable fashion has made it extremely useful in synthesis.⁸ Due to the concerted nature of this reaction, the stereochemical features of both the diene and the dienophile are conserved. While the transition metal-catalyzed [4 + 2] cycloaddition has been demonstrated to mitigate many reactivity problems associated with the Diels-Alder reaction, its stereochemical course, an issue of mechanistic and synthetic significance, has not been adequately evaluated.

In order to address this point, the relationship between starting diene geometry and product stereochemistry in the intramolecular nickel-catalyzed [4 + 2] cycloaddition was investigated. The 1*E*,3*Z*-dienyne **12** (Scheme 3) was prepared in a 40:60 mixture with its 1*E*,3*E*-dienyne isomer **6** using cinnamyl triphenylphosphonium chloride²⁵ under "salt-free" Wittig olefination conditions.²⁶ Since these two dienyne were chromatographically inseparable, the major isomer was removed by selective Diels-Alder reaction with maleic anhydride. The less reactive *E,Z*-isomer **12** was then easily separated from the intermolecular Diels-Alder adduct and isolated in pure form. The nickel(0)-catalyzed cycloaddition was carried out using the now standard conditions. Interestingly, diene **12** cyclized to a single product, **13**, of complementary stereochemistry to the cycloadduct (**9**) obtained in the metal-catalyzed cycloaddition of **6** (Scheme 2). *Thus, these results showed that diene stereochemistry is conserved in the course of this nickel-catalyzed intramolecular [4 + 2] cycloaddition.* Furthermore, the observed products are identical to what would be expected from the analogous Diels-Alder reactions but are obtained under substantially milder conditions (50 °C vs >270 °C).



Scheme 3

The identical connectivity of cycloaddition products **9** and **13** was proven by isolation of the same aromatization product, **14**, following individual DDQ treatment. The relative stereochemistry between the doubly-allylic centers was determined by the ¹H NMR homoallylic coupling signatures of these 1,4-cyclohexadienes.²⁷ When positioned in boat-like structures such as **9'**, *cis*-1,4-related hydrogens are known to give rise to large, long range coupling constants. The distinction between *cis* and *trans* 1,4-coupling constants in these types of systems is dependent upon the rigidity of the cyclohexadiene ring system, with fixed, full-boat conformations exhibiting 1,4-coupling constants as different as $J_{cis} = 12$ Hz and $J_{trans} = 4.7$ Hz.²⁸ In contrast, systems adopting more planar conformations give rise to comparable *cis* and *trans* homoallylic coupling constants, such as $J_{cis} = 8.3$ Hz and $J_{trans} = 7.5$ Hz. The observed coupling constants of 9.07 Hz for **9** and 5.28 Hz for **13**, fall squarely within the range of expected values, thereby allowing for the relative stereochemical assignment.



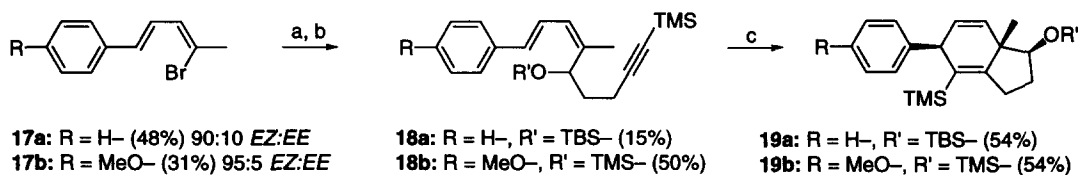
Scheme 4

A mechanistic hypothesis bearing on the complementary stereochemistry of *E,E*- and *E,Z*-dienyne cycloadditions is given in Scheme 4.²⁹ Initial coordination of the nickel catalyst with *E,E*-dienyne **6** should occur at the alkyne and at the internal double bond of the conformationally favored transoid diene. Cyclometallation to form the first carbon–carbon bond would place the styryl group on the same face of the nickelacyclopentene as the angular hydrogen (*syn* addition), giving complex **15** (R=H). In order for reductive elimination to a *cis,cis*-cyclohexadiene product to occur, the styryl group must first rotate past the angular

hydrogen, as shown in **15'**, and coordinate from its opposite π -face, as in **15''**. Reductive elimination from this η^1 -allyl nickelacycloheptadiene species, or its η^3 -allyl isomer, would then provide the η^2 -complex of product **9**. In the alternate case, complexation of the *E,Z*-dienyne **12** and cyclometallation, again by *syn* addition, should give **16** (*R*=H) and would place the styryl group on the *opposite face* from the angular hydrogen in the nickelacyclopentene. Requisite rotation of the styryl group, this time past the methylene bridge of the newly formed five-membered ring, as in **16'**, would give the nickelacycloheptadiene complex **16''**. Finally, reductive elimination would form the η^2 -complex of product **13**. Thus, while involving a multistep sequence with reversible processes, the metal-catalyzed cycloaddition proceeds with complete retention of stereochemistry.

Introduction of quaternary centers. Previous studies found that the metal-catalyzed [4 + 2] cycloaddition of *E,E*-dienes cannot be used to create systems with an angular alkyl substituent.^{3h} This potentially limits the scope of this otherwise effective process, as fused ring systems containing quaternary methyl groups, in particular, are ubiquitous structural motifs in natural and non-natural organic systems, such as steroids and terpenoids.⁹ Based on the preceding mechanistic analysis, however, an approach to the extension of this methodology to the preparation of angularly substituted products was made possible. Thus, in the key reorganizational phase of a cycloaddition beginning with an *E,E*-dienyne, the pendant vinyl group must rotate through a conformation such as that found in **15'** (Scheme 4) where it is in close proximity to the angular *R* group. The degree of steric interaction between these two groups must be insignificant when *R* = H, since the reaction proceeds to completion. Rotation in the opposite sense, past the nickel is precluded by the steric encumbrance of the ligand sphere. The mechanistic necessity of this rotation would explain why the inclusion of larger groups at the internal position of *E,E*-dienes could inhibit the cycloadditions. In these cases, the angular hydrogen is replaced by a more sterically demanding substituent, *R* in **15'**, which raises the barrier for the required rotation. The observation that an *R* group as small as even a methyl group completely prevents [4 + 2] cycloaddition,^{3h} suggests that the reaction is extremely sensitive to steric changes in this vicinity. In contrast, the *E,Z*-diene **12** would proceed through a path in which the vinyl group would rotate past the methylene bridge, as in **16'**, rather than past the *R* group. Due to the angle deformation in such *flattened* bicyclic systems, this methylene group poses less of a steric barrier to rotation than the *R* group in **15'**. As such, angularly substituted systems such as **16** should cyclize even when the *R* is an alkyl group. To test this point, the cyclization of **18a** was studied.

Preparation of this test substrate employed the *Z*-selective bromo-Wittig methodology of Smithers³⁰ as the key step (Scheme 5). Lithium–halogen exchange of $\text{Ph}_3\text{P}^+\text{CBr}_2(\text{CH}_3)\text{Br}^-$ gave rise to the bromophosphorane which underwent a Wittig reaction with cinnamaldehyde to give an inseparable 90:10 mixture of *E,Z*-bromodiene **17a** and the *E,E*-bromodiene. Lithium halogen exchange of these vinyl bromides with *t*-BuLi, followed by condensation with a 4-pentynal gave the corresponding, somewhat unstable allylic alcohols, from which the *E,Z*-isomer could be isolated in pure form. Finally, TBS protection gave the desired 4-methyl-1*E*,3*Z*-dienyne **18a**. The yields were not optimized in this mechanistic study.



Reaction Conditions: (a) i. *t*-BuLi, THF, –78 °C; ii. MgBr_2 , Et_2O , PhH; iii. 5-trimethylsilyl-4-pentynal; (b) TBSOTf or TMS-imid; (c) 20 mol% $\text{Ni}(\text{acac})_2$, 40 mol% Et_2AlOEt , 60 mol% $\text{P}(\text{O}-\text{C}_3\text{H}_7\text{F}_6)_3$, cyclohexane, 0.01M, 80 °C

Scheme 5

When the nickel-catalyzed cycloaddition of **18a** was attempted under standard conditions at 50 °C, no reaction was observed. Upon warming to 80 °C, however, the reaction proceeded to give a single new product having a 3H singlet in the ^1H NMR spectrum at 1.02 ppm. To ensure that this cycloaddition was not simply a

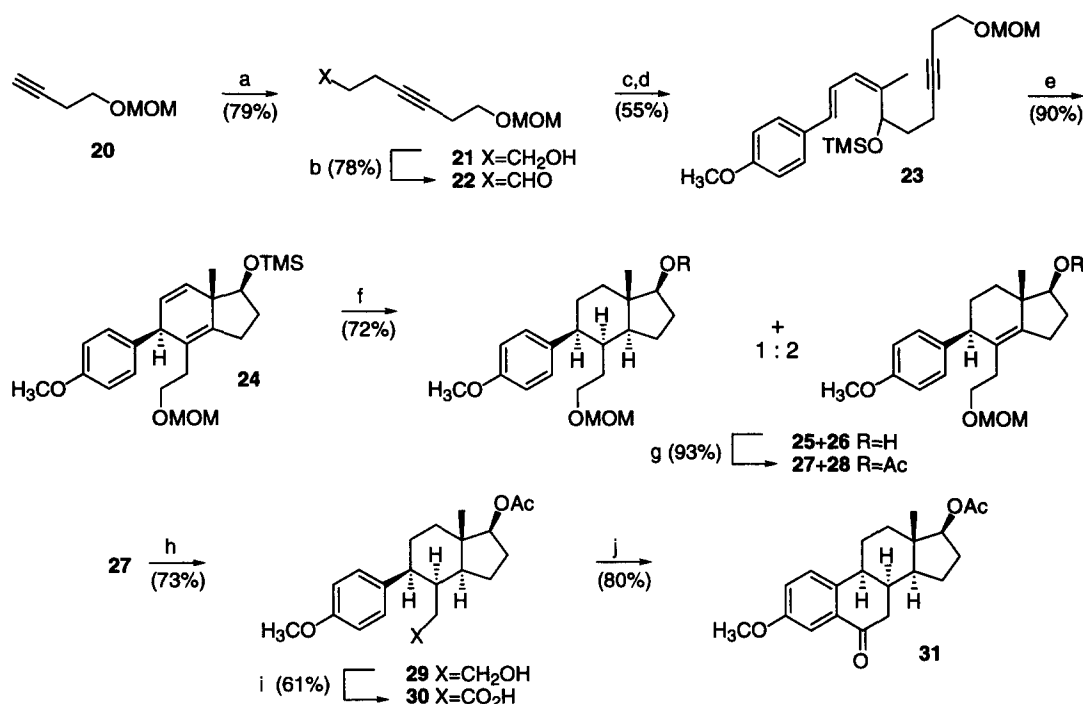
Diels–Alder reaction, a thermal control was performed. When heated in a sealed tube, diyne **18a** began to decompose at 150 °C. The half-life for this thermal decomposition was calculated to be 14.7 h at 150 °C, and no traces of cycloaddition product were observed. At the time, the stereochemical relationship between the phenyl and methyl groups in **19a** was made only by analogy to the unsubstituted product **13**. Similarly, while the reaction appeared to be completely diastereoselective, the relative stereochemistry of the silyloxy substituent was unknown. The mechanistic model which led to this success also predicts a significant degree of diastereoselectivity when allylic substituents are present. As shown for **16** (Scheme 4) the reversible first carbon–carbon bond formation which places the bulky silyloxy substituent in the energetically more favorable pseudoequatorial (or *exo*) position, would lead to a product having this group *syn* to the angular methyl, as in **19a**. Moreover, if the substituent were to be oriented in the pseudoaxial position, it would pose an additional obstacle to the required vinyl rotation. Subsequent investigations of analogous systems showed that the actual relative stereochemistry was indeed the one predicted and indicated for **19a**. These stereochemical determinations will be fully discussed in the next section.

Initial Synthetic Application to Steroid and Vitamin D Analogs. The capability of this new method to assemble angularly-substituted hydrindane derivatives containing three stereocenters was ideally suited for application to the synthesis of the CD ring systems of steroid or vitamin D derivatives. A particularly easy entry into the A-ring aromatic steroid framework was envisaged, since most of the structural features of these systems had already been assembled in the formation of **19a**, and in addition this synthetic approach would serve as a chemical correlation to prove the relative stereochemistry of the cycloaddition product.

To begin these investigations, the effect of a *p*-methoxy-substituent upon the key [4 + 2] cycloaddition was explored. Although this electronic perturbation was expected to have little effect upon the outcome of these reactions, based on the results discussed in the first section, the effect of an electron-donating group was unknown. As a quick check of the viability of this process when a *p*-methoxy group was included in the starting materials, a diyne analogous to **18a** was prepared (Scheme 5). This time, however, the synthetic problems which were ignored in the preparation of **18a** were addressed. Wittig reaction between *p*-methoxy cinnamaldehyde and the bromoethylphosphorane gave the *E,Z*-vinyl bromide **17b** along with its *E,E*-isomer in an 95:5 ratio. Previously, removal of the undesired isomer was postponed until the allylic alcohol stage, at which point product instability caused a significant decrease in yield. Isomer separation was achieved at this earlier step by recrystallization of the vinyl bromide from methanol/water to give isomerically pure **17b**. Alternatively, the isomeric impurity could be carried through to the cycloaddition, after which the unreacted *E,E*-starting material could be separated from the desired cycloadduct.³¹

Condensation of the vinyl lithiate derivative of **17b** with the alkynyl aldehyde required substantial optimization since, under the original conditions, deprotonation of the aldehyde was more facile than nucleophilic addition. This problem was alleviated by transmetalation of the vinyl lithiate with freshly prepared³² MgBr₂ prior to introduction of the aldehyde. In this way, an 88% yield of the allylic alcohol was achieved. Finally, all TBS silylating agents investigated were found to be either unreactive (TBS-Cl, TBS-imid., MTBSTFA) or to cause decomposition of the starting material (TBS-OTf). To overcome these problems, the TMS-protected diyne **18b** was prepared instead, using TMS-imidazole. Gratifyingly, nickel-catalyzed [4 + 2] cycloaddition proceeded with substrate **18b** to give the *p*-methoxy-substituted product **19b** in an unoptimized yield of 54%. In contrast, in the absence of catalyst, **18b** does not undergo cycloaddition but rather decomposes with a half-life of 14.7 h at 150 °C.

Once the cycloaddition step was shown to tolerate a methoxy substituent, the alkynyl appendage was modified to include the additional two carbons required to complete the steroidal framework (Scheme 6). The magnesium salt of MOM-protected 3-butyne-1-ol **20**³³ was alkylated with oxetane to give the differentially protected heptyne diol **21**. Oxidation under Swern–Moffatt conditions provided aldehyde **22**. Finally, following the earlier methodology, condensation of this aldehyde with the vinyl magnesium derivative of **17b** gave an allylic alcohol which was converted directly to its TMS derivative, **23**, without intermediate purification. By way of this sequence, the diyne substrate for the key cycloaddition step could be prepared in five linear steps from commercially available 3-butyne-1-ol.



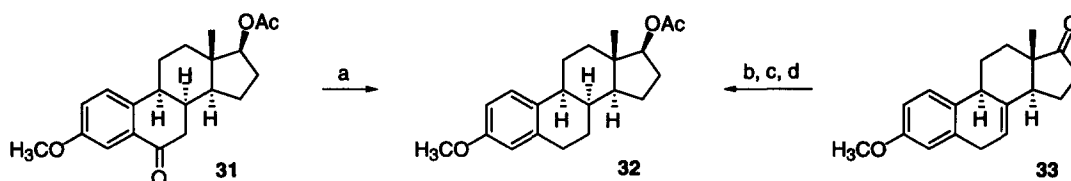
Reaction Conditions: (a) EtMgBr , PhH , $0^\circ\text{C} \rightarrow \text{rt}$, oxetane, reflux; (b) Swern; (c) **17b**, $t\text{-BuLi}$, THF , -78°C , ii. MgBr_2 , Et_2O , PhH , iii. inverse addition; (d) TMS-imid; (e) 10 mol% Ni(COD)_2 , 20 mol% $\text{P}(\text{O}i\text{-C}_3\text{HF}_6)_3$, cyclohexane, 0.01M, 80°C ; (f) 10% Pd/C , EtOH , 1 atm H_2 , rt; (g) Ac_2O , DMAP, pyr : $\text{CH}_2\text{Cl}_2 = 1:1$, rt; (h) $B\text{-Br}$ catechol borane, CH_2Cl_2 , rt; (i) Jones' reagent, acetone, rt; (j) i. SOCl_2 , $\text{rt} \rightarrow 50^\circ\text{C}$, ii. AlCl_3 , PhH , rt

Scheme 6

The nickel-catalyzed cycloaddition of this substrate was optimized, giving cycloadduct **24** as a single product in 90% yield. The most effective nickel source for this particular reaction was found to be Ni(COD)_2 . When the $\text{Ni(acac)}_2/\text{Et}_2\text{AlOEt}$ system was used, a somewhat lower yield of 68% was obtained. It was also possible to minimize the catalyst loading to 10 mol%, but when it was reduced to 5 mol% the reaction did not initiate. As usual, the contrasting thermal control reaction showed no evidence of cycloaddition, but instead gave decomposition products with a half-life of 109 h at 175°C .

Catalytic hydrogenation of this cycloadduct, gave a 1:2 ratio of doubly-reduced product **25** to singly-reduced product **26** with cleavage of the TMS protecting group in a combined yield of 72%. Precedent for this α -selectivity exists in the hydrogenation of 8,14-didehydro-estrone to 8 α -isoestrone.³⁴ Although these two hydrogenation products could not be separated by chromatography, acetylation allowed for isolation of the pure acetates, **27** and **28**. Completion of the steroid synthesis was initiated with selective removal of the MOM group of **27** with B -bromo catechol borane.³⁵ The resultant primary alcohol, **29**, was then oxidized under Jones conditions to give the carboxylic acid **30**. Formation of the acid chloride with thionyl chloride,³⁶ followed by Friedel–Crafts acylation³⁷ gave the tetracyclic steroid **31**.

To verify the product stereochemistry, **31** was subjected to hydrogenolysis³⁸ of the benzylic ketone to provide (\pm)-8 α -isoestradiol, 17 β -acetate, 3-methyl ether, **32** (Scheme 7) which was correlated with an authentic sample obtained from equilin 3-methyl ether, **33**.^{39,40,41} The two isoestrone derivatives, prepared from different routes, had identical ^1H NMR spectra, IR spectra, and high-resolution mass spectroscopy fragmentation patterns. A 1:1 mixture co-eluted on GC.



Reaction Conditions: (a) 10% Pd/C, 1 atm H₂, AcOH, 5% HClO₄; (b) 10% Pd/C, 1 atm H₂, EtOH, PhH; (c) NaBH₄, EtOH, reflux; (d) Ac₂O, DMAP, Pyr:CH₂Cl₂ = 1:1.

Scheme 7

In summary, a short synthetic route to an A-ring aromatic steroid, utilizing a nickel(0)-catalyzed intramolecular [4 + 2] cycloaddition as the key step, was achieved. The cycloaddition precursor **23** was assembled in five linear steps from commercially available 3-butyne-1-ol using a selective bromo-Wittig reaction to set the required *Z*-geometry. Importantly, when treated with *in situ* prepared nickel(0) catalyst, this dienyne was converted in 90% yield to only one cycloadduct, the desired hydrindane **24**, possessing natural steroidal stereochemistry at the pro-C9, C13, and C17 centers. *The utility of this transition metal catalyzed process is strikingly contrasted by the reaction of dienyne 23 in the absence of a catalyst which proceeds with a half-life of 109 h at 175 °C to provide only decomposition products.* Furthermore, the mechanistic model which initiated these studies predicted correctly the high degree and relative sense of the diastereoselectivity observed in this cycloaddition. This initial study demonstrates the synthetic potential of the nickel-catalyzed process through a concise and conceptually unique approach to the Vitamin D and steroid CD-ring system.

Conclusion

Several mechanistically and synthetically important aspects of the nickel-catalyzed [4 + 2] cycloaddition of dienyne are established in this study. First, the nickel-catalyzed cycloaddition is shown to proceed in several cases in which the corresponding Diels-Alder cycloaddition either fails or requires forcing conditions. Second, the process is relatively insensitive to electronic effects, thereby accommodating a greater range of substrates than would be expected for the conventional Diels-Alder cycloaddition. Third, while proceeding through a multistep pathway, the metal-catalyzed cycloaddition occurs with conservation of stereochemistry, thereby retaining an important synthetic feature of the Diels-Alder cycloaddition. Fourth, the cycloadditions of methyl substituted *Z*-alkenes can be used to produce products containing angular methyl groups. In addition, the cycloadditions of substrates with allylic substituents are found to occur with high diastereoselectivities, as illustrated in a preliminary study of the utility of this process in the synthesis of steroid and Vitamin D analogs.

Experimental Section.

General. The following general procedures were used in all reactions unless otherwise noted. Reactions were carried out in flame-dried or oven-dried glassware sealed with rubber septa at room temperature under a atmosphere of dry nitrogen. Ether, THF, DME, benzene, and cyclohexane were distilled from sodium-benzophenone ketyl under nitrogen. Toluene was distilled from sodium without added benzophenone. Acetonitrile, CH₂Cl₂, triethylamine, diisopropylamine, and pyridine were distilled from calcium hydride under nitrogen. Commercially available Ni(COD)₂ from Strem was obtained as a flocculent light yellow solid. A small amount of the solid complex was transferred in a dry box under nitrogen to a Schlenk flask then diluted with THF in order to obtain a 0.05–0.1 M solution which was stable indefinitely when stored in the freezer at -20 °C. Ni(acac)₂ was dried periodically in a vacuum desiccator over P₂O₅ and transferred in the open atmosphere. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed using EM silica gel 60 (230–240 mesh). All new compounds were colorless oils or liquids unless otherwise indicated. Melting points were determined with a Thomas–

Hoover melting point apparatus and are uncorrected. NMR spectra were measured in Fourier transform mode on a Varian XL-400 (^1H at 400 MHz, ^{13}C at 100 MHz), a Varian Gemini-300 (^1H at 300 MHz, ^{13}C at 75 MHz), or Varian Gemini-200 (^1H at 200 MHz, ^{13}C at 50 MHz) magnetic resonance spectrometer. Proton NMR spectra are reported as chemical shifts in parts-per-million (ppm) downfield from a tetramethylsilane internal standard (0.00 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. Infrared spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer (FTIR) and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the University of California, San Francisco, or at the University of California, Riverside. Reported mass values are within the error limits of ± 13 millimass units. Elemental analyses (%C, %H, %N) were determined by Desert Analytics, Tucson, Arizona. Reported atomic percentages are within the error limits of $\pm 0.4\%$. Unless otherwise indicated, the transition metal-catalyzed cycloaddition reactions provided single product diastereomers within the detection limits of ^1H NMR spectrometry.

(2E,4E)-10-Trimethylsilyl-deca-2,4-dien-9-ynoic acid ethyl ester (1). To a solution of THF (10 mL), HMPA (5 mL), and diisopropylamine (1.04 mL, 7.42 mmol, 1.25 equiv) at -78°C was added *n*-butyllithium (4.64 mL, 1.6 M solution, 7.42 mmol, 1.25 equiv) and the reaction was stirred for 10 min. Triethyl 4-phosphonocrotonate (1.58 mL, 7.13 mmol, 1.2 equiv.) was then added *via* syringe and the solution turned a dark orange color. Within 5 min 6-trimethylsilyl-5-hexynal (999.5 mg, 5.94 mmol, 1 equiv) was added *via* cannula in THF (1 mL). The color dissipated with addition of the aldehyde and the reaction was stirred at -78°C for 2.5 h. The reaction was quenched by cannula transfer into a 125 mL Erlenmeyer flask containing 1 M HCl (30 mL) and ether (30 mL) at 25°C . The organic layer was washed with water (2 x 15 mL) to remove any remaining HMPA. The ethereal fraction was dried over MgSO_4 , filtered, and concentrated. Purification by flash filtration through a 4 in. plug of silica (Et_2O) followed by MPLC (4% EtOAc /hexanes) gave the desired product **1** (759.1 mg, 48%). ^1H -NMR (CDCl_3 , 300 MHz) δ 7.26 (dd, $J = 15.3, 10.3$ 1H), 6.27–6.04 (m, 2H), 5.80 (d, $J = 15.4$, 1H), 4.20 (q, $J = 7.1$, 2H), 2.33–2.20 (m, 4H), 1.66 (qn, $J = 7.2$, 2H), 1.30 (t, $J = 7.1$, 3H), 0.15 (s, 9H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 167.10, 144.65, 142.99, 129.04, 119.57, 106.49, 85.10, 60.12, 31.79, 27.44, 19.21, 14.25, 0.08 ppm. FTIR (neat) 2958.3, 2901.8, 2361.7, 2174.3, 1888.3, 1715.7, 1644.1, 1617.8, 1446.6, 1367.9, 1329.0, 1302.7, 1248.4, 1195.5, 1152.1, 1131.8, 1036.4, 1000.3, 842.9, 760.0, 698.4, 639.2 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{Si}$: 264.1546 (M^+); Found: 264.1553. Elemental Analysis: Calc. for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{Si}$: C, 68.13%; H, 9.15%. Found: C, 68.37%; H, 9.47%.

(5R*,7aS*)-4-Trimethylsilyl-2,3,5,7a-tetrahydro-1H-indene-5-carboxylic acid ethyl ester (2). To an acid-washed, base-washed, 10 mL Schlenk flask was added diyne **1** (24.8 mg, 0.094 mmol, 1 equiv), tris-(*ortho*fluorophenyl) phosphite (7.0 mg, 0.019 μmol , 0.2 equiv), $\text{Ni}(\text{acac})_2$ (4.8 mg, 0.019 mmol, 0.2 equiv), and cyclohexane (9.38 mL). Diethylaluminum ethoxide (23.4 μL , 1.6 M in toluene) was added and the reaction was warmed to 72°C . The clear suspension of green $\text{Ni}(\text{acac})_2$ slowly changed to a bright yellow homogeneous solution and after 19 h the reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (Et_2O) followed by flash chromatography (30% benzene/hexanes) gave the 1,4-cyclohexadiene **2** (16.6 mg, 67%). ^1H -NMR (CDCl_3 , 300 MHz) δ 5.98 (dt, $J = 10.0, 2.7$, 1H), 5.68 (dt, $J = 10.0, 2.7$, 1H), 4.15 (q, $J = 7.1$, 2H), 3.78 (ddd, $J = 10.3, 2.6, 2.6$, 1H), 2.66 (dm, $J = 9.9$, 1H), 2.47–2.37 (m, 2H), 2.05–1.93 (dm, $J = 9.9$, 1H), 1.88–1.67 (m, 2H), 1.28 (t, $J = 7.1$, 3H), 0.12 (s, 9H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 175.2, 155.5, 130.0, 124.5, 122.2, 61.2, 47.6, 41.5, 31.6, 30.5, 22.7, 14.6, -0.1 ppm. IR (neat) 2950, 2865, 1737, 1623, 1446, 1359, 1310, 1250, 1165, 1098, 1055, 1032, 924, 882, 840, 690, 615 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{Si}$: 264.1546 (M^+); Found: 264.1551.

(E)-(3-phenyl-allyl)-phosphonic acid diisopropyl ester (3). Cinnamyl chloride (7.5004 g, 49.14 mmol, 1 equiv) and triisopropyl phosphite (12.12 mL, 49.14 mmol, 1 equiv) were heated to reflux in a 130°C bath overnight. The isopropyl chloride byproduct was removed on the rotary evaporator and the resulting crude product was purified by flash chromatography (5% Et_2O /hexanes until all unreacted cinnamyl chloride was eluted, followed by 100% Et_2O then 100% EtOAc) to give the cinnamyl phosphonate **3** (10.8786 g, 78%) as a clear viscous oil. ^1H -NMR (CDCl_3 , 300 MHz) δ 7.40–7.20 (m, 5H), 6.52 (dd, $J = 15.8, 5.1$, 1H), 6.17 (ddd,

$J=15.8$, 7.6, 7.3, 1H), 4.80–4.52 (m, 2H), 2.77 (d, $J=7.5$, 1H), 2.70 (d, $J=7.6$, 1H), 1.32 (at, $J=5.9$, 12H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 137.13, 134.58, 134.38, 128.52, 127.44, 126.17, 119.58, 119.42, 70.17, 70.08, 32.81, 30.93, 23.64, 23.56 ppm. FTIR (neat) 3460, 2978.8, 1385.6, 1247.0, 1106.2, 983.3, 746.2 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{15}\text{H}_{23}\text{O}_3\text{P}$: 282.1385 (M^+); Found: 282.1383.

(E)-4-[(3-Diisopropoxy-phosphoryl)-propenyl]-benzoic acid ethyl ester (4). To a resealable thick-walled pressure tube was added palladium(II) acetate (147 mg, 0.655 mmol, 0.03 equiv), triphenylphosphine (344 mg, 1.31 mmol, 0.06 equiv), ethyl 4-bromobenzoate (5.00 g, 21.8 mmol, 1 equiv), diisopropyl allylphosphonate (4.50 g, 21.8 mmol, 1 equiv), and HMPA (7.33 mL). After flushing with nitrogen, diisopropylamine (6.12 mL, 43.6 mmol, 2 equiv) was added, the tube was sealed, heated to 130 °C, and stirred for 7 h by which time the golden-colored solution had turned black. This mixture was diluted with ether (200 mL), washed with 1 M HCl (2 x 125 mL), dried over MgSO_4 , filtered, and concentrated. Purification was achieved by flash chromatography (100% Et_2O) followed by Kugelrohr distillation (180 °C at 5 mmHg) to remove the volatile impurities. The remaining product was dissolved in EtOAc, decolorized with activated charcoal and filter through paper. Concentration gave the cinnamyl phosphonate **4** (1.55 g, 20%) as a yellow oil. ^1H -NMR (CDCl_3 , 300 MHz) δ 7.99 (d, $J=8.3$, 2H), 7.41 (d, $J=8.3$, 2H), 6.56 (dd, $J=16.0$, 5.2, 1H), 6.30 (ddd, $J=15.8$, 7.6, 7.2, 1H), 4.74–4.64 (m, 2H), 4.38 (q, $J=7.1$, 2H), 2.79 (d, $J=7.6$, 1H), 2.72 (d, $J=7.2$, 1H), 1.39 (t, $J=7.1$, 3H), 1.30 (at, $J=6.6$, 12H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 166.71, 141.66, 133.96, 133.77, 130.13, 129.73, 126.23, 126.19, 122.73, 122.57, 70.58, 70.49, 60.77, 33.21, 31.33, 23.85, 23.81, 14.06 ppm. IR (neat) 3415, 2975, 2920, 2850 2235, 1515, 1607, 1465, 1452, 1385, 1373, 1302, 1180, 1108, 1012, 986, 904, 891, 762, 734 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{18}\text{H}_{27}\text{O}_5\text{P}$: 354.1596 (M^+); Found: 354.1639.

(E)-[3-(4-Chloro-phenyl)-allyl]-phosphonic acid diisopropyl ester (5). To a solution of 4-chlorocinnamic acid, (2.007 g, 10.99 mmol, 1 equiv) in THF (16.6 mL) at -7 °C (ice/salt bath) was added triethylamine (1.532 mL, 10.99 mmol, 1 equiv). Ethyl chloroformate (1.05 mL, 10.99 mmol, 1 equiv) was added over 5 min. After stirring for 1 h the salts were filtered off and rinsed with THF. The filtrate was placed in a 100 mL 3-neck flask fitted with a reflux condenser. Sodium borohydride (1.59 g, 41.98 mmol, 3.8 equiv) was added slowly at 0–10 °C followed by methanol (6.68 mL) added *via* syringe pump overnight. This mixture was quenched by addition of 6 M HCl (40 mL), diluted with CHCl_3 (50 mL), and extracted with CHCl_3 (3 x 15 mL). The combined organic fractions were dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography (40% EtOAc/hexanes) gave 4-chlorocinnamyl alcohol (1.2233 g, 66%) as colorless crystals. ^1H -NMR (CDCl_3 , 300 MHz) δ 7.37–7.23 (m, 4H), 6.59 (d, $J=16.0$, 1H), 6.35 (dt, $J=15.9$, 5.6, 1H), 4.34 (dd, $J=5.8$, 5.6, 2H), 1.45 (t, $J=5.9$, 1H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 135.46, 133.52, 129.95, 129.44, 128.90, 127.79, 63.36 ppm. FTIR (neat) 3320.2, 2862.2, 1491.0, 1404.6, 1088.3, 1012.2, 967.5, 848.7, 796.1 cm^{-1} . HRMS (EI) Calculated for $\text{C}_9\text{H}_9\text{ClO}$: 170.0312 (M^+ ; ^{37}Cl); Found: 170.03072

To a mixture of sodium iodide (1.30 g, 8.71 mmol, 1.2 equiv) and acetonitrile (9 mL) was added TMSCl (1.105 mL, 8.71 mmol, 1.2 equiv) and the color changed from clear to a milky yellow. To this was added 78 mL water followed by 4-chlorocinnamyl alcohol (1.223 g, 7.25 mmol, 1 equiv) in acetonitrile (3 mL). The reaction was stirred at rt for 3.5 h, after which it was diluted with Et_2O (10 mL), washed with water (10 mL) and then saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL). The combined aqueous layers were back-extracted with ether (2 x 10 mL) and the combined organic fractions were dried over MgSO_4 , filtered, and concentrated. The unpurified light-brown crystalline iodide (1.7369 g) was carried on to the next step without purification.

The unpurified iodide and triisopropyl phosphite (1.77 mL, 7.18 mmol) were heated to reflux in a 130 °C bath overnight. After removal of the isopropyl iodide byproduct on the rotary evaporator, purification by flash chromatography (40% EtOAc/hexanes) gave the cinnamyl phosphonate **5** (1.5677 g, 68% for two steps) as a clear viscous oil. ^1H -NMR (CDCl_3 , 300 MHz) δ 7.28 (s, 4H), 6.47 (dd, $J=15.9$, 5.1, 1H), 6.15 (ddd, $J=15.9$, 7.7, 7.6, 1H), 4.80–4.62 (m, 2H), 2.76 (d, $J=7.7$, 1H), 2.68 (d, $J=7.6$, 1H), 1.32 (at, $J=6.7$, 12H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 135.64, 135.59, 133.32, 133.12, 128.71, 127.38, 120.41, 120.25, 70.27, 70.18, 32.78, 30.90, 23.63, 23.56 ppm. FTIR (neat) 3450, 2972, 1722, 1651, 1510, 1384, 1263, 1169, 1131, 1104, 992, 891, 784, 706 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{15}\text{H}_{22}\text{ClO}_3\text{P}$: 316.0995 (M^+); Found: 316.0992.

(6E,8E)-Trimethyl-(9-phenyl-nona-6,8-dien-1-ynyl)-silane (6). To a solution of diisopropylamine (453 μ L, 3.23 mmol, 1.1 equiv) and THF (5 mL) at 0 °C was added *n*-butyllithium (2.05 mL, 1.58 M in hexane, 3.23 mmol, 1.1 equiv) followed after 5 min by HMPA (5 mL) then cinnamyl phosphonate **3** (830.0 mg, 2.94 mmol, 1 equiv) in THF (2.5 mL) *via* cannula. After 15 min the yellow-orange solution was cooled to –65 °C in a dry ice/chloroform slurry and 6-trimethylsilyl-5-hexynal was added dropwise in THF (2.5 mL) *via* cannula. After 5 h the reaction was diluted with hexanes (25 mL), and washed with saturated aqueous NH_4Cl (15 mL) and water (15 mL). The combined aqueous layers were extracted with hexanes (3 x 10 mL) and the combined organic fractions were dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography (100% hexanes) gave the aryl diyne **6** (393 mg, 50%, *E,E,Z* = 91:9 by NMR). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.31 (dm, *J*=7.1, 2H), 7.22 (dm, *J*=7.8, 2H), 7.18–7.09 (m, 1H), 6.68 (dd, *J*=15.6, 10.3, 1H), 6.38 (d, *J*=15.6, 1H), 6.16 (dd, *J*=15.2, 10.3, 1H), 5.74 (dt, *J*=15.2, 7.6, 1H), 2.21–2.14 (m, 4H), 1.63–1.53 (m, 2H), 0.09 (s, 9H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 137.89, 134.50, 131.56, 130.63, 129.44, 128.70, 127.30, 126.34, 107.16, 84.88, 31.53, 28.00, 19.04, –0.20 ppm. FTIR (neat) 2957.0, 2173.0, 1248.9, 986.9, 841.8, 758.4, 691.8 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{18}\text{H}_{24}\text{Si}$: 268.1647 (M^+); Found: 268.1649.

(1E,3E)-4-(9-Trimethylsilyl-nona-1,3-dien-8-ynyl)-benzoic acid ethyl ester (7). To a solution of diisopropylamine (471 μ L, 3.36 mmol, 1.1 equiv), HMPA (20 mL), and THF (40 mL) at 0 °C was added *n*-butyllithium (2.00 mL, 1.64 M in hexane, 3.27 mmol, 1.07 equiv) followed after 5 min by cinnamyl phosphonate **4** (1.0838 g, 3.06 mmol, 1 equiv) in THF (10 mL) *via* cannula. After 15 min the deep red solution was cooled to –65 °C in a dry ice/chloroform slurry and 6-trimethylsilyl-5-hexynal was added in THF (10 mL) *via* cannula. After 8 h the reaction was quenched by addition of saturated aqueous NaHCO_3 (25 mL), diluted with Et_2O (50 mL), and washed with NaHCO_3 solution (30 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic fractions were dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography (3% EtOAc /hexanes) gave the aryl diyne **7** (556.4 mg, 53%). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.98 (d, *J*=8.4, 2H), 7.42 (d, *J*=8.4, 2H), 6.85 (dd, *J*=15.7, 10.4, 1H), 6.47 (d, *J*=15.8, 1H), 6.24 (dd, *J*=15.1, 10.4, 1H), 5.88 (dt, *J*=15.0, 7.2, 1H), 4.37 (q, *J*=7.1, 2H), 2.32–2.22 (m, 4H), 1.66 (qn, *J*=7.2, 2H), 1.39 (t, *J*=7.1, 3H), 0.16 (s, 9H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 166.72, 142.32, 136.41, 131.87, 131.28, 130.06, 129.56, 129.2, 126.06, 107.01, 84.99, 60.65, 31.56, 27.87, 19.02, 14.01, –0.21 ppm. IR (neat) 2955, 2895, 2175, 1718, 1604, 1413, 1367, 1274, 1240, 1179, 1108, 1022, 989, 845, 696, 637 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{21}\text{H}_{28}\text{O}_2\text{Si}$: 340.1858 (M^+); Found: 340.1874.

(6E,8E)-[9-(4-Chlorophenyl)-nona-6,8-dien-1-ynyl]-trimethyl-silane (8). To a solution of diisopropylamine (337 μ L, 2.41 mmol, 1.1 equiv) in THF (5 mL) at 0 °C was added *n*-butyllithium (1.52 mL, 1.58 M in hexane, 2.41 mmol, 1.1 equiv) followed after 5 min by HMPA (5 mL) then chloro-cinnamyl phosphonate **5** (693.3 mg, 2.19 mmol, 1 equiv) in THF (2.5 mL) *via* cannula. After stirring for 15 min the yellow-orange solution was cooled to –65 °C in a dry ice/chloroform slurry and 6-trimethylsilyl-5-hexynal was added dropwise in THF (2.5 mL) *via* cannula. After 5 h the reaction was diluted with hexanes (25 mL), and washed with saturated aqueous NH_4Cl (15 mL) and water (15 mL). The combined aqueous layers were extracted with hexanes (3 x 10 mL) and the combined organic fractions were dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography (100% hexanes) gave the chloro-aryl diyne **8** (432.9 mg, 65%, *E,E,Z* = 94:6 by NMR). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.33–7.21 (m, 4H), 6.72 (dd, *J*=15.7, 10.3, 1H), 6.40 (d, *J*=15.7, 1H), 6.22 (dd, *J*=14.7, 10.5, 1H), 5.82 (dt, *J*=15.1, 7.6, 1H), 2.29–2.18 (m, 4H), 1.67 (m, 2H), 0.16 (s, 9H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 136.46, 135.28, 132.97, 131.33, 130.12, 129.28, 128.94, 127.52, 107.13, 84.99, 31.58, 27.98, 19.08, –0.15 ppm. FTIR (neat) 2956.3, 2173.1, 1489.8, 1248.6, 1090.9, 985.9, 841.8, 759.4 cm^{-1} . HRMS (EI) Calc. for $\text{C}_{18}\text{H}_{23}\text{ClSi}$: 304.1228 (M^+ ; ^{37}Cl); Found: 304.1198.

(5S*,7aS*)-Trimethyl-(5-phenyl-2,3,5,7a-tetrahydro-1H-indene-4-yl)-silane (9). To an acid-washed, base-washed 25 mL Schlenk flask was added diyne **6** (40.1 mg, 0.149 mmol, 1 equiv) and $\text{Ni}(\text{acac})_2$ (7.7 mg, 0.030 mmol, 0.2 equiv). Cyclohexane (14.9 mL), tris-(hexafluoroisopropyl)phosphite (47.7 mg, 0.090 mmol, 0.6 equiv), and diethylaluminum ethoxide (37.3 μ L, 1.6 M in toluene) were added sequentially under a positive nitrogen flow and the reaction was stirred at rt for 1 h. The clear suspension of green

Ni(acac)₂ slowly changed to a golden yellow homogeneous solution which was warmed to 50 °C and stirred overnight. The reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (Et₂O) followed by flash chromatography (100% isooctane) gave the 1,4-cyclohexadiene **9** (19.5 mg, 49%). ¹H-NMR (CDCl₃, 300 MHz) δ 7.29–7.24 (m, 2H), 7.19–7.11 (m, 3H), 5.74 (ddd, J=10.0, 2.5, 2.5, 1H), 5.56 (ddd, J=10.0, 2.9, 2.6, 1H), 4.03 (ddd, J=9.1, 2.4, 2.1, 1H), 2.80–2.68 (m, 1H), 2.54–2.33 (m, 2H), 2.12–2.01 (m, 1H), 1.90–1.70 (m, 2H), 1.37–1.21 (m, 1H), –0.15 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 152.91, 146.27, 131.26, 129.51, 128.30, 126.58, 126.23, 123.75, 46.98, 40.77, 32.00, 30.19, 22.09, 0.02 ppm. FTIR (neat) 3022.0, 2951.0, 2864.7, 2360.5, 1617.4, 1489.2, 1450.8, 1245.9, 1047.5, 877.6, 834.4, 759.9, 732.4, 700.1 cm^{–1}. HRMS (DEI) Calc. for C₁₈H₂₄Si: 268.1647 (M⁺); Found: 268.1643.

(5S*,7aS*)-4-(4-Trimethylsilyl-2,3,5,7a-tetrahydro-1H-inden-5-yl)-benzoic acid ethyl ester (10). To an acid-washed, base-washed, 10 mL Schlenk flask was added dienyne **7** (23.5 mg, 0.070 mmol, 1 equiv) and Ni(acac)₂ (3.5 mg, 0.014 mmol, 0.2 equiv). Under a positive nitrogen flow, cyclohexane (6.9 mL) and tris-(hexafluoroisopropyl) phosphite (22.0 mg, 0.041 mmol, 0.6 equiv) were added. Diethylaluminum ethoxide (17.3 μL, 1.6 M in toluene) was added *via* gastight syringe and the reaction was stirred at rt for 1 h. The clear suspension of green Ni(acac)₂ slowly changed to a bright yellow homogeneous solution which was then warmed to 50 °C and stirred overnight. The reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (Et₂O) followed by flash chromatography (5% Et₂O/hexanes) gave the 1,4-cyclohexadiene **10** (13.5 mg, 57%). ¹H-NMR (CDCl₃, 300 MHz) δ 7.96 (d, J=8.3, 2H), 7.20 (d, J=8.3, 2H), 5.77 (ddd, J=10.0, 2.4, 2.4, 1H), 5.50 (ddd, 10.0, 2.8, 2.8, 1H), 4.36 (q, J=7.1, 2H), 4.10 (dm, J=9.1, 1H), 2.82–2.67 (m, 1H), 2.49–2.34 (m, 2H), 2.13–2.02 (m, 1H), 1.94–1.31 (m, 2H), 1.38 (t, J=7.1, 3H), 1.33–1.20 (m, 1H), –0.14 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 166.95, 153.64, 151.72, 130.41, 129.70, 129.34, 128.62, 125.97, 124.46, 60.57, 47.06, 40.79, 31.80, 30.24, 22.04, 13.98, 0.01 ppm. FTIR (neat) 2952.7, 1719.1, 1607.6, 1414.0, 1366.3, 1274.1, 1247.5, 1173.8, 1100.1, 1020.7, 837.2 cm^{–1}. HRMS (EI) Calculated for C₂₁H₂₈O₂Si: 340.1859 (M⁺); Found: 340.1844

(5S*,7aS*)-[5-(4-Chlorophenyl)-2,3,5,7a-tetrahydro-1H-inden-4-yl]-trimethylsilane (11). To an acid-washed, base-washed, 25 mL Schlenk flask was added dienyne **8** (35.8 mg, 0.125 mmol, 1 equiv) and Ni(acac)₂ (6.4 mg, 0.025 mmol, 0.2 equiv). Under a positive nitrogen flow, cyclohexane (12.5 mL) and tris-(hexafluoroisopropyl) phosphite (39.9 mg, 0.075 mmol, 0.6 equiv) were added. Diethylaluminum ethoxide (31.2 μL, 1.6 M in toluene) was added *via* gastight syringe and the reaction was stirred at rt for 1 h. The clear suspension of green Ni(acac)₂ slowly changed to a golden yellow homogeneous solution which was warmed to 50 °C and stirred overnight. The reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (Et₂O) followed by flash chromatography (100% hexanes) gave the 1,4-cyclohexadiene **11** (22.6 mg, 63%). ¹H-NMR (CDCl₃, 300 MHz) δ 7.24 (d, J=8.4, 2H), 7.06 (d, J=8.4, 2H), 5.75 (ddd, J=10.0, 2.4, 2.4, 1H), 5.50 (ddd, J=10.0, 2.7, 2.7, 1H), 4.01 (dm, J=9.0, 1H), 2.80–2.65 (m, 1H), 2.54–2.31 (m, 2H), 2.13–2.00 (m, 1H), 1.92–1.70 (m, 2H), 1.35–1.16 (m, 1H), –0.13 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 153.52, 145.04, 132.02, 130.89, 130.82, 128.49, 126.35, 124.21, 46.47, 40.83, 31.94, 30.32, 22.15, 0.09 ppm. FTIR (neat) 2952.4, 1618.0, 1489.6, 1404.8, 1246.4, 1088.3, 1015.3, 834.3, 751.8 cm^{–1}. HRMS (EI) Calc. for C₁₈H₂₃ClSi: 304.1228 (M⁺; ³⁷Cl); Found: 304.1226.

(6Z,8E)-Trimethyl-(9-phenyl-nona-6,8-dien-1-ynyl)-silane (12). To a solution of cinnamyl triphenylphosphonium chloride (1.886 g, 3.72 mmol, 1 equiv) in THF (60 mL) at 0 °C was added sodium bis-(trimethylsilyl)amide (3.91 mL, 1.0 M in THF, 3.91 mmol, 1.05 equiv). After 30 min, 6-trimethylsilyl-5-hexynal (690 mg, 4.10 mmol, 1.1 equiv) was added in THF (5 mL) dropwise *via* cannula to the deep-red solution and the reaction was warmed to rt and stirred for 1 h. This mixture was diluted with hexanes (20 mL) and washed with water (3 x 25 mL). The combined aqueous layers were back-extracted with CHCl₃ (3 x 25 mL) and the combined organic fractions were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by addition of hexanes to precipitate most of the Ph₃PO, followed by flash chromatography (100% hexanes) to give a 6:4 ratio of *E,E* and *E,Z* dienyne **6** and **12** (700.3 mg, 70%).

A solution of **6** and **12** (332.1 mg, 1.24 mmol, 1 equiv) and recrystallized maleic anhydride (102.8 mg, 1.05 mmol, 0.85 equiv) in toluene (20 mL) was heated to reflux overnight. The maleic anhydride adducts were

separated from the desired unreacted pure *E,Z* dienyne **12** by flash chromatography (100% hexanes). ¹H-NMR (CDCl₃, 300 MHz) δ 7.46 (d, J=7.4, 2H), 7.34 (ddm, J=7.6, 7.1, 2H), 7.25 (dm, J=7.1, 1H), 7.12 (ddd, J=15.6, 11.1, 1.0, 1H), 6.58 (d, J=15.4, 1H), 6.24 (dd, J=11.0, 10.9, 1H), 5.54 (dt, J=10.7, 7.9, 1H), 2.48–2.40 (m, 2H), 2.32 (t, J=7.0, 2H), 1.74–1.64 (qn, J=7.2, 2H), 0.20 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 137.75, 132.62, 131.89, 129.89, 128.74, 127.58, 126.53, 124.37, 107.20, 84.80, 28.29, 26.67, 19.04, –0.15 ppm. FTIR (neat) 3026.2, 2957.4, 2173.1, 1491.9, 1448.9, 1248.7, 1020.6, 984.3, 945.2, 841.6, 758.8, 730.2, 691.1 cm^{–1}. HRMS (EI) Calculated for C₁₈H₂₄Si: 268.1647 (M⁺); Found: 268.1632.

(5R*,7aS*)-Trimethyl-(5-phenyl-2,3,5,7a-tetrahydro-1H-indene-4-yl)-silane (13). To an acid-washed, base-washed, 10 mL Schlenk flask was added dienyne **12** (27.7 mg, 0.103 mmol, 1 equiv) and Ni(acac)₂ (5.3 mg, 0.021 mmol, 0.2 equiv). Under a positive nitrogen flow, cyclohexane (10.3 mL) and tris-(hexafluoroisopropyl)phosphite (32.9 mg, 0.062 mmol, 0.6 equiv) were added. Diethylaluminum ethoxide (26.0 μL, 1.6 M in toluene) was added *via* gastight syringe and the reaction was stirred at rt for 1 h. The clear suspension of green Ni(acac)₂ slowly changed to a golden yellow homogeneous solution which was warmed to 50 °C and stirred overnight. The reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (Et₂O) followed by flash chromatography (100% isooctane) gave the 1,4-cyclohexadiene **13** (14.6 mg, 53%). ¹H-NMR (CDCl₃, 300 MHz) δ 7.30–7.26 (m, 2H), 7.21–7.15 (m, 3H), 5.95 (ddd, J=9.5, 5.2, 2.9, 1H), 5.85 (dd, J=9.5, 1.6, 1H), 4.10 (dd, J=5.3, 4.8, 1H), 2.87–2.75 (m, 1H), 2.68–2.47 (m, 2H), 2.10 (ddd, J=12.3, 6.6, 5.8, 1H), 1.94–1.84 (m, 1H), 1.82–1.74 (m, 1H), 1.35–1.22 (m, 1H), 0.01 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 155.03, 145.50, 131.54, 128.57, 127.97, 127.64, 126.72, 126.08, 47.24, 42.59, 32.26, 30.33, 23.65, –0.56 ppm. FTIR (neat) 3021.9, 2952.0, 2360.9, 1614.7, 1490.5, 1449.6, 1246.1, 1043.5, 883.7, 834.8, 749.5, 722.5, 697.7 cm^{–1}. HRMS (DEI) Calculated for C₁₈H₂₄Si: 268.1647 (M⁺); Found: 268.1652.

Trimethyl-(5-phenyl-3H-inden-4-yl)-silane (14). To a solution of 1,4-cyclohexadiene **9** (or alternately epimer **13**) (13.3 mg, 0.050 mmol, 1 equiv) in benzene (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (22.5 mg, 0.099, 2 equiv) as an orange powder and the mixture was heated to reflux. After 2 h, GC indicated complete consumption of SM and a 1:1 mixture of new products. These were determined to be an inseparable mixture of indane and indene by NMR. The mixture was refluxed with DDQ for an additional 45 h to effect complete conversion to the indene. Purification by flash filtration through a plug of silica (hexanes) and flash chromatography (100% isooctane) gave the indene **14** (3.3 mg, 25%) as a clear oil. ¹H-NMR (CDCl₃, 300 MHz) δ 7.43 (d, J=7.7, 1H), 7.39–7.32 (m, 1H), 7.36 (dd, J=5.2, 1.9, 2H), 7.32–7.26 (m, 2H), 7.14 (d, J=7.7, 1H), 6.93 (ddd, J=5.6, 2.0, 1.9, 1H), 6.62 (ddd, J=5.6, 2.1, 2.0, 1H), 3.54 (dd, J=1.9, 1.9, 2H), 0.03 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 150.09, 146.39, 145.75, 143.22, 134.44, 133.35, 131.68, 129.93, 128.82, 127.77, 126.95, 121.18, 41.38, 1.56 ppm. FTIR (neat) 1247.9, 920.7, 832.2, 763.1, 701.6 cm^{–1}. HRMS (EI) Calculated for C₁₈H₂₀Si: 264.1334 (M⁺); Found: 264.1322.

(1E,3Z)-1-(4-methoxyphenyl)-4-bromo-1,3-pentadiene (17b). To THF (189 mL) at –78 °C was added *t*-BuLi (21.99 mL, 1.72 M in pentane, 37.8 mmol, 2.2 equiv) followed by 1,1-dibromoethyltriphenylphosphonium bromide (10.00 g, 18.91 mmol, 1.1 equiv) as a suspension in THF (20 mL) *via* cannula. After 20 min the resulting blood-red suspension turned to a light orange color. After a further 40 min, 4-methoxycinnamaldehyde (2.80 g, 17.19 mmol, 1 equiv) was added in THF (25 mL) dropwise *via* cannula. The color became deeper and a white turbidity developed. The reaction was warmed to rt and stirred overnight. The white ppt. was filtered off and the filtrate was concentrated to 1/4 of the original volume. Hexanes were then added with vigorous stirring and the precipitated Ph₃PO was again removed by filtration. The filtrate was flushed through a plug of silica (95:5 hexanes/ethyl acetate), to remove the bulk of the remaining Ph₃PO, and concentrated *in vacuo*. The crude product was purified by recrystallization (MeOH/H₂O) and dried in a vacuum desiccator over P₂O₅ to give the desired product **17b** (519.5 mg, 31% yield, *E,Z:E,E* = 95:5) as a white powder. An analytical sample was prepared by multiple recrystallizations. ¹H-NMR (CDCl₃, 300 MHz) δ 7.39 (dm, J=8.5, 2H), 6.87 (dm, J=8.8 2H), 6.87 (dd, J=15.4, 10.1) 6.58 (d, J=15.7, 1H), 6.37 (dm, J=9.4, 1H), 3.81 (s, 3H), 2.41 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 159.77, 133.38, 130.09, 128.83, 127.99, 124.77, 123.12, 114.22, 55.20, 28.98 ppm. FTIR (neat) 2960.5, 1600.6, 1509.0, 1294.2, 1255.4, 1172.0,

1080.7, 1032.1, 964.6, 871.3, 851.9, 815.7, 598.8, 534.8, 515.2 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{12}\text{H}_{13}\text{BrO}$: 254.0129 (M^+ ; ^{81}Br); Found: 254.0101. Elemental Analysis Calculated for $\text{C}_{12}\text{H}_{13}\text{BrO}$: C, 56.94%; H, 5.18%; Br, 31.57%. Found: C, 57.22%; H, 5.43%; Br, 31.46%.

(1E,3Z)-[5-(*tert*-Butyl-dimethyl-silyloxy)-4-methyl-9-trimethylsilyl-nona-1,3-dien-8-ynyl]-benzene (18a). To a solution of Z-vinyl bromide **17a** (100.7 mg, 0.451 mmol, 1.25 equiv) prepared from cinnamaldehyde, in THF (5 mL) at -78°C was added *t*-butyllithium (617 μL , 1.61 M in pentane, 0.993 mmol, 2.75 equiv). The reaction was stirred for 1 h and the color changed from yellow to blue to a deep emerald hue. 5-Trimethylsilyl-4-pentynal (55.7 mg, 0.361 mmol, 1 equiv) was added in THF (1 mL) dropwise *via* cannula. After 3 h the color returned to a light yellow and the mixture was quenched by addition of sat. aq. NH_4Cl (10 mL) and was washed with sat. aq. NaCl (5 mL). The combined aqueous layers were back-extracted with ether (2 x 5 mL) and the combined organic fractions were dried over MgSO_4 , filtered, and concentrated. The crude product was purified by flash chromatography (4% EtOAc/hexanes) to give the desired allylic alcohol (34.0 mg, 32%). ^1H -NMR (CDCl_3 , 300 MHz) δ 7.40 (d, $J=7.2$, 2H), 7.31 (dd, $J=7.2$, 7.2, 2H), 7.23 (dm, $J=7.2$, 1H), 7.10 (dd, $J=15.4$, 11.3, 1H), 6.49 (d, $J=15.4$, 1H), 6.10 (d, $J=11.3$, 1H), 5.02 (dd, $J=6.5$, 5.8, 1H), 2.48–2.26 (m, 2H), 1.98–1.80 (m, 1H), 1.86 (s, 3H), 1.80–1.64 (m, 2H), 0.16 (s, 9H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 139.88, 137.72, 132.34, 128.76, 128.13, 127.59, 126.52, 123.74, 106.74, 85.33, 69.06, 33.63, 17.92, 16.30, -0.20 ppm. FTIR (neat) 3396.0, 2957.8, 2172.8, 1449.8, 1249.7, 1050.9, 960.1, 842.4, 748.8, 692.9 cm^{-1} . HRMS (EI) Calculated for $\text{C}_{19}\text{H}_{26}\text{OSi}$: 298.1753 (M^+); Found: 298.1757.

To a solution of the allylic alcohol (25.0 mg, 0.0838 mmol, 1 equiv) and triethylamine (23 μL , 0.168 mmol, 2 equiv) in methylene chloride (2.0 mL) at 0°C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (20 μL , 0.088 mmol, 1.05 equiv). The reaction was allowed to warm to rt and was diluted with CH_2Cl_2 (5 mL), quenched by addition of water (5 mL), and washed with water (5 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated. Evaluation of the unpurified reaction mixture by NMR showed only 89% conversion of the alcohol SM. Purification by flash chromatography (100% hexanes) gave the desired silyl ether **18a** (15.1 mg, 44%). ^1H -NMR (CDCl_3 , 300 MHz) δ 7.40 (d, $J=7.2$, 2H), 7.30 (dd, $J=7.2$, 7.2, 2H), 7.22 (dm, $J=7.2$, 1H), 7.12 (dd, $J=15.3$, 11.3, 1H), 6.46 (d, $J=15.2$, 1H), 6.01 (d, $J=11.3$, 1H), 4.92 (dd, $J=8.4$, 4.9, 1H), 2.41–2.18 (m, 2H), 1.89–1.73 (m, 1H), 1.80 (s, 3H), 1.69–1.56 (m, 2H), 0.90 (s, 9H), 0.18 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 141.40, 137.97, 131.65, 128.75, 127.42, 126.74, 126.45, 124.16, 107.27, 84.92, 69.24, 34.80, 25.62, 18.22, 17.95, 16.15, -0.15 , -5.09 , -5.30 ppm. FTIR (neat) 2955.5, 2855.9, 2172.9, 141.7, 1250.1, 1066.3, 987.2, 958.3, 839.2, 776.3, 746.5, 690.8 cm^{-1} . HRMS (EI) Calc. for $\text{C}_{25}\text{H}_{40}\text{OSi}_2$: 412.2618 (M^+); Found: 412.2617.

(1E,3Z)-1-(4-methyl-9-trimethylsilyl-5-trimethylsilyloxy-nona-1,3-dien-8-ynyl)-4-methoxy-benzene (18b). To a solution of Z-vinyl bromide **17b** (245.1 mg, 0.968 mmol, 1.33 equiv) and TMEDA (292 μL , 1.936 mmol, 2.67 equiv) in THF (5 mL) at -78°C was added *t*-butyllithium (1.08 mL, 1.7 M in pentane, 1.840 mmol, 2.53 equiv) in one squirt. The reaction was stirred for exactly 5 min, the color changed from yellow to blue to a deep emerald hue, and freshly prepared MgBr_2 (1.94 mL, 1.0 M in Et_2O and benzene, 1.936 mmol, 2.67 equiv) was added dropwise. After 10 min, 5-trimethylsilyl-4-pentynal (114.8 mg, 0.726 mmol, 1 equiv) was added in THF (3 mL) dropwise *via* cannula and the reaction was warmed to rt. The mixture was washed with water (2 x 10 mL). The organic fraction was dried over MgSO_4 , filtered, and concentrated. Flash chromatography (4% EtOAc/hexanes) gave the allylic alcohol (205.0 mg, 88%). ^1H -NMR (CDCl_3 , 300 MHz) δ 7.33 (dm, $J=8.7$, 2H), 6.96 (dd, $J=15.4$, 11.3, 1H), 6.84 (dm, $J=8.8$, 2H), 6.43 (d, $J=15.4$, 1H), 6.06 (d, $J=11.3$, 1H), 5.03–4.94 (m, 1H), 3.81 (s, 3H), 2.46–2.24 (m, 2H), 1.97–1.81 (m, 1H), 1.83 (s, 3H), 1.80 (d, $J=3.3$, 1H), 1.79–1.65 (m, 1H), 0.16 (s, 9H) ppm. ^{13}C -NMR (CDCl_3 , 75 MHz) δ 159.45, 138.57, 131.89, 130.53, 128.34, 127.73, 121.84, 114.18, 106.84, 85.23, 69.05, 55.17, 33.60, 17.85, 16.31, -0.17 ppm. FTIR (neat) 3434.2, 2956.9, 2172.5, 1603.9, 1510.1, 1442.0, 1303.2, 1249.1, 1174.5, 1034.3, 962.0, 842.5, 759.8, 639.9 cm^{-1} . HRMS (EI) Calc. for $\text{C}_{20}\text{H}_{28}\text{O}_2\text{Si}$: 328.1859 (M^+); Found: 328.1851.

To a solution of the allylic alcohol (205.0 mg, 0.656 mmol, 1 equiv) in CH_2Cl_2 (13 mL) was added trimethylsilyl imidazole (168 μL , 1.148 mmol, 1.75 equiv). After 80 min. the reaction was concentrated. Purification by flash chromatography (1% EtOAc/hexanes) on triethylamine-deactivated silica gel gave the

desired trimethylsilyl ether **18b** (161.1 mg, 61%). ¹H-NMR (CDCl₃, 300 MHz) δ 7.35 (dm, J=8.8, 2H), 6.98 (dd, J=15.4, 11.3, 1H), 6.85 (dm, J=8.8, 2H), 6.41 (d, J=15.4, 1H), 5.98 (d, J=11.3, 1H), 4.95 (dd, J=8.8, 4.7, 1H), 3.81 (s, 3H), 2.40–2.23 (m, 2H), 1.85–1.76 (m, 1H), 1.78 (s, 1H), 1.68–1.57 (m, 1H), 0.19 (s, 9H), 0.13 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 159.35, 140.01, 131.25, 130.76, 127.64, 126.79, 122.15, 114.172, 107.25, 84.88, 69.05, 55.18, 34.48, 18.16, 16.10, –0.11, –0.31 ppm. FTIR (neat) 2956.4, 2172.7, 1604.5, 1509.7, 1441.6, 1302.7, 1249.3, 1174.0, 1066.5, 1036.0, 988.8, 960.0, 873.9, 841.0, 758.9, 638.6 cm^{–1}. HRMS (EI) Calculated for C₂₃H₃₆O₂Si₂: 400.2254; Found: 400.2260 Elemental Analysis: Calculated for C₂₃H₃₆O₂Si₂: C, 68.94%; H, 9.06%. Found: C, 68.96%; H, 8.99%.

(3S*,3aS*,6R*)-3-(tert-Butyl-dimethyl-silyloxy)-3a-methyl-6-phenyl-7-trimethylsilyl-2,3,3a,6-tetrahydro-1H-indene (19a). To an acid-washed, base-washed, 10 mL Schlenk flask was added dienyne **18a** (14.5 mg, 0.035 mmol, 1 equiv) and Ni(acac)₂ (1.8 mg, 0.007 mmol, 0.2 equiv). Under a positive nitrogen flow, cyclohexane (3.5 mL) and tris-(hexafluoroisopropyl)phosphite (11.2 mg, 0.021 mmol, 0.6 equiv) were added. Diethylaluminum ethoxide (8.8 μL, 1.6 M in toluene, 0.014 mmol, 0.4 equiv) was added *via* gastight syringe and the reaction was stirred at rt for 1 h. The clear suspension of green Ni(acac)₂ slowly changed to a golden yellow homogeneous solution which was warmed to 80 °C and stirred overnight. The reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (Et₂O) followed by flash chromatography (100% hexanes) gave the 1,4-cyclohexadiene **19a** (7.8 mg, 54%). ¹H-NMR (CDCl₃, 300 MHz) δ 7.32–7.19 (m, 2H), 7.18–7.125 (m, 3H), 5.79 (dd, J=9.5, 4.6, 1H), 5.70 (d, J=9.9, 1H), 4.06 (d, J=4.3, 1H), 3.75 (dd, J=9.3, 8.2, 1H), 2.74–2.61 (m, 1H), 2.55–2.41 (m, 1H), 1.99–1.86 (m, 1H), 1.81–1.66 (m, 1H), 1.02 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H), –0.05 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 155.45, 145.02, 130.52, 129.21, 128.57, 128.15, 125.98, 77.50, 77.20, 47.36, 45.53, 29.15, 26.33, 25.60, 19.22, 17.80, –0.58, –4.69, –5.20 ppm. FTIR (neat) 2954.9, 2856.5, 1462.4, 1248.1, 1107.0, 911.6, 835.4, 774.8, 728.4, 699.7 cm^{–1}. HRMS (EI) Calc. for C₂₅H₄₀OSi: 412.2618 (M⁺); Found: 412.2613.

(3S*,3aS*,6R*)-3-(Trimethylsilyloxy)-6-(4-methoxy-phenyl)-3a-methyl-7-trimethylsilyl-2,3,3a,6-tetrahydro-1H-indene (19b). To an acid-washed, base-washed, 10 mL Schlenk flask was added dienyne **18b** (18.9 mg, 0.047 mmol, 1 equiv) and Ni(acac)₂ (2.4 mg, 0.009 mmol, 0.2 equiv). Under a positive nitrogen flow, cyclohexane (4.7 mL) and tris-(hexafluoroisopropyl) phosphite (15.1 mg, 0.028 mmol, 0.6 equiv) were added. Diethylaluminum ethoxide (11.8 μL, 1.6 M in toluene, 0.019 mmol, 0.4 equiv) was added *via* gastight syringe and the reaction was stirred at rt for 1 h. The clear suspension of green Ni(acac)₂ slowly changed to a golden yellow homogeneous solution which was then warmed to 80 °C and stirred overnight. The reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (5% Et₂O/hexanes) followed by flash chromatography (5% Et₂O/hexanes) gave the 1,4-cyclohexadiene **19b** (10.2 mg, 54%). ¹H-NMR (CDCl₃, 300 MHz) δ 7.10 (d, J=8.6, 2H), 6.82 (d, J=8.5, 2H), 5.76 (dd, J=9.6, 4.7, 1H), 5.67 (d, J=9.7, 1H), 3.99 (d, J=4.1, 1H), 3.78 (s, 3H), 3.73 (dd, J=9.3, 8.3, 1H), 2.73–2.59 (m, 1H), 2.56–2.40 (m, 1H), 1.99–1.85 (m, 1H), 1.82–1.66 (m, 1H), 1.02 (s, 3H), 0.11 (s, 9H), –0.05 (s, 9H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 158.09, 155.10, 137.10, 130.12, 129.46, 129.07, 128.98, 113.91, 77.21, 55.08, 46.45, 45.16, 29.11, 26.27, 19.32, –0.10, –0.56 ppm. FTIR (neat) 2958.8, 2359.9, 1508.3, 1249.2, 1101.1, 912.8, 839.0 cm^{–1}. HRMS (EI) Calculated for C₂₃H₃₆O₂Si₂: 400.2254 (M⁺); Found: 400.2263.

7-Methoxymethoxy-hept-4-yn-1-ol (21). To a solution of 4-methoxymethoxy-but-1-yne (3.0105 g, 26.37 mmol, 1 equiv) in benzene (100 mL) at 0 °C was added ethylmagnesium bromide (8.79 mL, 3.0 M in Et₂O, 26.37 mmol, 1 equiv). The reaction was allowed to warm to rt, was stirred for 1 h, and the Et₂O was removed by short-path distillation. Oxetane (2.57 mL, 39.56 mmol, 1.5 equiv) was added *via* syringe, and the solution was heated to reflux overnight. The mixture was diluted with ether (50 mL), quenched by addition of sat. aq. NH₄Cl (30 mL), and washed with water (30 mL). The combined aqueous layers were back-extracted with Et₂O (3 x 20 mL) and the combined organic fractions were dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (33% EtOAc/hexanes) to give the alcohol **21** (3.5642 mL, 79%). ¹H-NMR (CDCl₃, 300 MHz) δ 4.66 (s, 2H), 3.73 (td, J=5.8, 5.2, 2H), 3.62 (t, J=6.8, 2H), 3.38 (s, 3H), 2.46 (tt, J=6.8, 2.4, 2H), 2.34 (t, J=4.9, 1H), 2.28 (tt, J=6.9, 2.4, 2H), 1.73 (qn, J=6.5, 2H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 96.27, 80.54, 77.32, 66.20, 61.52, 55.03, 31.19, 19.89, 15.05 ppm. FTIR (neat)

3422.4, 2935.9, 2883.7, 1439.3, 1382.3, 1338.0, 1208.1, 1150.4, 1111.1, 1072.1, 1029.6, 958.5, 917.7 cm^{-1} . HRMS (EI) Calculated for $\text{C}_9\text{H}_{16}\text{O}_3$: 172.1099 (M^+); Found: 172.1121

7-Methoxymethoxy-hept-4-ynal (22). To a solution of oxalyl chloride (398 μL , 4.56 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL) at -78°C was added DMSO (593 μL , 8.36 mmol, 2.2 equiv). After 30 min, heptynol **21** (654.7 mg, 3.80 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added dropwise *via* cannula and the solution was stirred for another 30 min. Triethylamine (1.45 mL, 10.45 mmol, 2.75 equiv) was then added and the reaction was allowed to warm to rt. After 3 h this mixture was quenched by addition of sat. aq. NaHCO_3 (10 mL) and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography (15% EtOAc/hexanes) gave heptynal **22** (503.1 mg, 78%). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 9.80 (t, $J=1.3$, 1H), 4.65 (s, 2H), 3.61 (t, $J=6.7$, 2H), 3.38 (s, 3H), 2.64 (td, $J=7.0$, 1.3, 2H), 2.53–2.41 (m, 4H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 201.26, 96.42, 79.02, 78.05, 66.14, 55.13, 42.67, 19.99, 11.85 ppm. FTIR (neat) 2927.4, 1726.6, 1387.6, 1207.7, 1150.0, 1110.5, 1072.4, 1027.6, 916.3 cm^{-1} . HRMS (EI) Calculated for $\text{C}_9\text{H}_{14}\text{O}_3$: 170.0943 (M^+); Found: 170.0925.

(2Z,4E)-[1-(6-Methoxymethoxy-hex-3-ynyl)-5-(4-methoxy-phenyl)-2-methyl-penta-2,4-dienyloxy]-trimethylsilane (23). To a solution of *Z*-vinyl bromide **17b** (1.0062 g, 3.97 mmol, 1.33 equiv) and DME (826 μL , 7.95 mmol, 2.67 equiv) in THF (100 mL) at -78°C was added *t*-butyllithium (4.13 mL, 7.55 mmol 1.83 M in pentane, 2.53 equiv) in one squirt. The reaction was stirred for exactly 5 min, the color had changed from yellow to blue to a deep emerald hue, and freshly prepared MgBr_2 (7.95 mL, 1.0 M in Et_2O and benzene, 7.95 mmol, 2.67 equiv) was added dropwise. After 15 min, aldehyde **22** (498.4 mg, 2.93 mmol, 1 equiv) was added in THF (10 mL) dropwise *via* cannula. The reaction was allowed to warm to rt and stir for 45 min. The mixture was quenched by addition of sat. aq. NH_4Cl (30 mL) and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic fractions were dried over Na_2SO_4 (do *not* substitute MgSO_4 here), filtered, and concentrated. The unstable allylic alcohol was carried on to the next step without purification.

To a solution of the allylic alcohol in CH_2Cl_2 (30 mL) was added trimethylsilyl imidazole (860 μL , 5.86 mmol, 2 equiv) After 15 min the reaction mixture was concentrated and purified by flash chromatography (5:15:80 $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{hexanes}$) on triethylamine-deactivated silica gel to give the desired trimethylsilyl ether **23** (665.4 mg, 55% for two steps). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.34 (dm, $J=8.7$, 2H), 7.00 (dd, $J=15.3$, 11.2, 1H), 6.87 (dm, $J=8.8$, 2H), 6.40 (d, $J=15.4$, 1H), 5.98 (d, $J=11.5$, 1H), 4.92 (dd, $J=8.4$, 5.1, 1H), 4.63 (s, 2H), 3.81 (s, 3H), 3.64 (t, $J=7.0$, 2H), 3.36 (s, 3H), 2.51 (tt, $J=7.0$, 2.3, 2H), 2.27–2.17 (m, 2H), 1.88–1.76 (m, 1H), 1.78 (s, 3H), 1.67–1.55 (m, 1H), 0.12 (s, 9H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 159.30, 140.13, 130.97, 130.80, 127.52, 126.64, 122.35, 114.18, 96.43, 81.04, 77.21, 69.41, 66.45, 55.22, 55.15, 35.10, 20.09, 18.17, 15.14, -0.28 ppm. FTIR (neat) 2952.6, 1604.1, 1510.1, 1441.4, 1249.3, 1174.3, 1150.2, 1110.3, 1070.5, 1035.4, 961.3, 874.5, 841.3 cm^{-1} . HRMS (EI) Calc. for $\text{C}_{24}\text{H}_{36}\text{O}_4\text{Si}$: 416.2383 (M^+); Found: 416.2382. Elemental Analysis: Calc. for $\text{C}_{24}\text{H}_{36}\text{O}_4\text{Si}$: C, 69.19%; H, 8.71%. Found: C, 69.40%; H, 8.73%.

(1S*,5R*,7aS*)-[4-(2-Methoxymethoxy-ethyl)-5-(4-methoxyphenyl)-7a-methyl-2,3,5,7a-tetrahydro-1H-inden-1-yloxy]-trimethylsilane (24). To an acid-washed, base-washed, 200 mL Schlenk flask was added diyne **23** (664.7 mg, 1.595 mmol, 1 equiv). Under a positive nitrogen flow, freshly distilled cyclohexane (160 mL) and tris(hexafluoroisopropyl) phosphite (170 mg, 0.319 mmol, 0.2 equiv) were added. Bis-1,5-cyclooctadiene nickel (2.13 μL , 0.075 M in THF, 0.160 mmol, 0.1 equiv) was added and the reaction was stirred at rt for 1 h. The clear solution slowly changed to a golden yellow solution which was then warmed to 80°C and stirred for 17.5 h. The reaction was quenched by opening to air and stirring for 30 min. Purification by flash filtration through a 1 in. plug of silica (20% $\text{Et}_2\text{O}/\text{hexanes}$) followed by flash chromatography (12.5% $\text{Et}_2\text{O}/\text{hexanes}$) gave the 1,4-cyclohexadiene **24** (597.2 mg, 90%). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.14 (dm, $J=8.6$, 2H), 6.84 (dm, $J=8.7$, 2H), 5.78 (dd, $J=9.7$, 1.2, 1H), 5.64 (dd, $J=9.7$, 4.2, 1H), 4.50 (dd, $J=8.1$, 6.5, 2H), 3.79 (d, $J=4.2$, 1H), 3.78 (s, 3H), 3.72 (dd, $J=9.4$, 8.1, 1H), 3.45–3.33 (m, 1H), 3.31–3.14 (m, 1H), 3.28 (s, 3H), 2.57–2.32 (m, 2H), 2.32–2.14 (m, 2H), 1.96–1.83 (m, 1H), 1.79–1.63 (m, 1H), 1.09 (s, 3H), 0.11 (s, 9H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 158.15, 139.63, 135.38, 130.92, 129.31, 127.67, 126.41, 113.88, 96.13, 77.73, 65.89, 55.24, 55.02, 47.37, 45.30, 31.52, 29.06, 23.33, 20.47, 0.21 ppm. FTIR (neat) 2954.8, 1608.5, 1509.1, 1465.0, 1376.0, 1300.4, 1251.1, 1148.5, 1107.8, 1069.0, 1036.3, 914.5, 893.2, 840.1, 748.2 cm^{-1} . HRMS (EI)

Calculated for $C_{24}H_{36}O_4Si$: 416.2383 (M^+); Found: 416.2385. Elemental Analysis: Calculated for $C_{24}H_{36}O_4Si$: C, 69.19%; H, 8.71%. Found: C, 68.93%; H, 8.79%.

(1S*,3aS*,4S*,5S*,7aS*)-Acetic acid 4-(2-methoxymethoxy-ethyl)-5-(4-methoxyphenyl)-7a-methyloctahydroinden-1-yl ester (27) and (1S*,5R*,7aS*)-Acetic acid 4-(2-methoxymethoxy-ethyl)-5-(4-methoxyphenyl)-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-1-yl ester (28). A 100 mL flask containing 1,4-cyclohexadiene **24** (129.2 mg, 0.310 mmol, 1 equiv), 10% palladium-on-carbon (66 mg, 0.062 mmol, 0.2 equiv), and absolute ethanol (25 mL) was fitted with a hydrogen balloon. The fine black suspension was stirred vigorously overnight under an atmosphere of H_2 . This mixture was flushed through a 1 in plug of packed celite (Et_2O) and concentrated. Flash chromatography (50% Et_2O /hexanes) gave an inseparable 1:2 mixture of free alcohols **25** and **26** (76.9 mg, 72% combined yield).

To a solution of the alcohols (346.4 mg, 1.00 mmol, 1 equiv), 4-dimethylaminopyridine (12.2 mg, 0.100 mmol, 0.1 equiv), and pyridine (10 mL) in CH_2Cl_2 (10 mL) was added acetic anhydride (283 μL , 3.00 mmol, 3 equiv) dropwise. After 3.75 h. The reaction was diluted with CH_2Cl_2 (50 mL) and washed with aq. $CuSO_4$ (6 x 25 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic fractions were dried over $MgSO_4$, filtered, and concentrated. MPLC (3% Et_2O/CH_2Cl_2) gave the two acetates in a combined yield of 93%. Pure samples of doubly- and singly-hydrogenated materials could be obtained at this stage by a difficult separation as **27** and **28**, or after the MOM-deprotection with greater ease to separate **29**.

Data for compound **27**: 1H -NMR ($CDCl_3$, 300 MHz) δ 7.13 (dm, $J=8.6$, 2H), 6.84 (dm, $J=8.7$, 2H), 4.64 (dd, $J=9.2$, 7.9, 1H), 4.32 (d, $J=6.4$, 1H, A of AB), 4.28 (d, $J=6.4$, 1H, B of AB), 3.79 (s, 3H), 3.17 (s, 3H), 2.79 (ddd, $J=12.9$, 3.6, 3.6, 1H), 2.59 (td, $J=9.1$, 7.4, 1H), 2.39 (td, $J=9.6$, 4.8, 1H), 2.29–2.14 (m, 1H), 2.06 (s, 3H), 2.05–1.90 (m, 1H), 1.88–1.76 (m, 3H), 1.76–1.63 (m, 2H), 1.63–1.47 (m, 3H), 1.43–1.23 (m, 2H), 0.92 (s, 3H) ppm. ^{13}C -NMR ($CDCl_3$, 75 MHz) δ 171.12, 157.91, 136.65, 128.30, 113.61, 96.03, 82.58, 68.37, 55.23, 54.85, 48.53, 46.81, 42.08, 39.61, 37.73, 27.09, 25.44, 23.05, 22.38, 21.19, 13.43 ppm. FTIR (neat) 2929.7, 2876.2, 2360.1, 2339.7, 1733.2, 1610.6, 1512.3, 1455.8, 1374.0, 1247.3, 1178.4, 1149.8, 1109.0, 1032.8, 916.8, 832.1 cm^{-1} . HRMS (EI) Calculated for $C_{23}H_{34}O_5$: 390.2406 (M^+); Found: 390.2403.

Data for compound **28**: 1H -NMR ($CDCl_3$, 300 MHz) δ 7.06 (dm, $J=8.6$, 2H), 6.83 (dm, $J=8.7$, 2H), 4.66 (dd, $J=10.3$, 7.8, 1H), 4.48 (d, $J=6.6$, 1H, A of AB), 4.46 (d, $J=6.6$, 1H, B of AB), 3.79 (s, 3H), 3.35 (td, $J=9.3$, 5.5, 1H), 3.30–3.16 (m, 2H), 3.26 (s, 3H), 2.55–2.33 (m, 2H), 2.25–2.11 (m, 2H), 2.08 (s, 3H), 2.02–1.85 (m, 2H), 1.84–1.60 (m, 3H), 1.43–1.25 (m, 1H), 1.11 (s, 3H) ppm. ^{13}C -NMR ($CDCl_3$, 75 MHz) δ 171.03, 157.89, 140.54, 138.04, 129.05, 128.92, 113.83, 96.02, 82.50, 65.42, 55.22, 54.97, 45.46, 42.99, 34.69, 30.99, 30.70, 26.36, 24.04, 21.19, 18.95 ppm. FTIR (neat) 2928.8, 2876.5, 1736.8, 1610.1, 1510.3, 1462.2, 1440.5, 1370.4, 1243.6, 1174.7, 1149.5, 1107.5, 1033.6, 829.0 cm^{-1} . Elemental Analysis: Calc. for $C_{23}H_{32}O_5$: C, 71.11%; H, 8.30%. Found: C, 71.36%; H, 8.27%. HRMS (EI) Calc. for $C_{23}H_{32}O_5$: 388.2250 (M^+); Found: 388.2256.

(1S*,3aS*,4S*,5S*,7aS*)-Acetic acid 4-(2-hydroxy-ethyl)-5-(4-methoxyphenyl)-7a-methyloctahydroinden-1-yl ester (29). To a solution of MOM ether **27** (35.6 mg, 0.091 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added *B*-bromocatecholborane (683 μL , 0.2 M in CH_2Cl_2 , 0.137 mmol, 1.5 equiv) dropwise. After 3 h, the mixture was quenched by addition of water (1 mL), diluted with CH_2Cl_2 (10 mL), and washed with 10% NaOH (3 x 5 mL). The combined aqueous layers were extracted back-extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic fractions were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (60% Et_2O /pentane) gave the desired alcohol **29** (23.0 mg, 73%). 1H -NMR ($CDCl_3$, 300 MHz) δ 7.13 (dm, $J=8.6$, 2H), 6.84 (dm, $J=8.7$, 2H), 4.64 (dd, $J=9.1$, 7.9, 1H), 3.79 (s, 3H), 2.79 (ddd, $J=12.8$, 3.9, 3.8, 1H), 2.72 (dd, $J=9.2$, 7.9, 1H), 2.60 (td, $J=9.1$, 5.5, 1H), 2.29–2.13 (m, 1H), 2.06 (s, 3H), 2.00–1.77 (m, 4H), 1.75–1.48 (m, 5H), 1.42–1.25 (m, 2H), 0.92 (s, 3H) ppm. ^{13}C -NMR ($CDCl_3$, 75 MHz) δ 171.12, 157.86, 136.72, 128.28, 113.61, 82.54, 63.49, 55.17, 48.50, 46.81, 42.09, 39.70, 37.71, 28.58, 27.07, 23.05, 22.40, 21.16, 13.47 ppm. FTIR (neat) 3435.2, 2931.4, 2864.3, 2360.6, 2338.4, 1733.3, 1610.3, 1582.0, 1512.0, 1466.3, 1373.5, 1246.5, 1179.2, 1109.0, 1032.7, 906.0, 832.5, 771.3 cm^{-1} . HRMS (EI) Calculated for $C_{21}H_{30}O_4$: 346.2144 (M^+); Found: 346.2151.

(1S*,3aS*,4S*,5S*,7aS*)-[1-Acetoxy-5-(4-methoxyphenyl)-7 α -methyl-octahydroindene-4-yl]-acetic acid (30). To a solution of alcohol **29** (18.7 mg, 0.054 mmol, 1 equiv) in acetone (5 mL) was added freshly prepared Jones reagent (1.12 g CrO₃, 2.0 mL H₂O, 1 mL conc. H₂SO₄) dropwise by pipette until an orange color persisted. After 10 min, this mixture was quenched by dropwise addition of isopropanol until the color turned a light green. The suspension was diluted with Et₂O (10 mL) and washed with water (2 x 5 mL). The combined aq. layers were back-extracted with CHCl₃ (3 x 10 mL). The combined organic fractions were dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography (35% EtOAc/hexanes followed by 1% AcOH/EtOAc) gave acid **30** (12.0 mg, 61%) as a white powder. ¹H-NMR (CDCl₃, 300 MHz) δ 7.11 (dm, J=8.7, 2H), 6.79 (dm, J=8.7, 2H), 4.64 (dd, J=9.2, 7.5, 1H), 3.74 (s, 3H), 2.86 (ddd, J=12.8, 4.0, 3.8, 1H), 2.74–2.65 (m, 1H), 2.30 (dd, J=16.7, 5.5, 1H), 2.25–2.15 (m, 1H), 2.12–2.01 (m, 1H), 2.07 (s, 3H), 1.98–1.81 (m, 2H), 1.74–1.48 (m, 4H), 1.40–1.25 (m, 2H), 0.93 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 179.00, 171.11, 158.06, 135.24, 128.68, 113.45, 82.30, 55.08, 47.73, 46.21, 41.98, 39.24, 37.29, 30.34, 27.02, 23.26, 22.19, 21.17, 13.40 ppm. FTIR (neat) 2926.4, 2872.1, 1736.5, 1731.7, 1707.9, 1611.2, 1512.7, 1371.6, 1285.7, 1246.2, 1179.4, 1033.2, 833.3 cm⁻¹. HRMS (EI) Calc. for C₂₁H₂₈O₅: 360.1936 (M⁺); Found: 360.1928.

(8S*,9S*,13S*,14S*,17S*)-Acetic acid 3-methoxy-13-methyl-6-oxo-7,8,9,11,12,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-17-yl ester [(\pm)-6-Oxo-17 β ,8 α -isoeestradiol, 17-acetate, 3-methyl ether] (31). To acid **30** (12.0 mg, 0.033 mmol, 1 equiv) was added thionyl chloride (excess: 15 drops). The solution was warmed to 50 °C for 2.5 h and the unreacted SOCl₂ was removed under vacuum. The crude acid chloride was dissolved in benzene (4.0 mL) and AlCl₃ (6.3 mg, 0.047 mmol, 1.4 equiv) was added. After 10 min. the mixture was diluted with Et₂O (10 mL), washed with 1 N HCl (2 x 5 mL), and the combined aq. layers were back-extracted with CHCl₃ (3 x 5 mL). The combined organic fractions were dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography (25% Et₂O/pentane) gave the benzylic ketone **31** (9.2 mg, 80%) as a white powder. ¹H-NMR (CDCl₃, 300 MHz) δ 7.47 (d, J=2.9, 1H), 7.22 (d, J=8.5, 1H), 7.10 (dd, J=8.5, 2.9, 1H), 4.65 (dd, J=8.9, 8.2, 1H), 3.84 (s, 3H), 2.85–2.73 (m, 1H), 2.72–2.62 (m, 1H), 2.60–2.49 (m, 1H), 2.30–2.16 (m, 1H), 2.07 (s, 3H), 1.87–1.66 (m, 6H), 1.61–1.50 (m, 2H), 1.50–1.36 (m, 1H), 0.97 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 198.33, 171.02, 158.20, 140.85, 132.34, 130.38, 122.19, 108.64, 82.04, 55.48, 47.09, 41.91, 41.57, 37.06, 36.82, 35.77, 27.30, 26.79, 21.86, 21.17, 13.49 ppm. FTIR (neat) 2935.0, 2873.0, 1735.2, 1683.4, 1608.2, 1493.9, 1421.5, 1381.5, 1362.4, 1322.6, 1278.1, 1243.7, 1032.7, 874.1, 830.7, 756.6 cm⁻¹. HRMS (EI) Calc. for C₂₁H₂₆O₄: 342.1831 (M⁺); Found: 342.1834.

(8S*,9S*,13S*,14S*,17S*)-Acetic acid 3-methoxy-13-methyl-7,8,9,11, 12,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-17-yl ester [(\pm)-17 β , 8 α -Isoestradiol, 17-acetate, 3-methyl ether] (32). A 25 mL flask containing keto acetate **31** (8.2 mg, 0.024 mmol, 1 equiv), acetic acid (3 mL), 10% Pd/C catalyst (7.6 mg, 0.007 mmol, 0.3 equiv), and 60% HClO₄ (5 drops) was fitted with a hydrogen balloon. The fine black suspension was stirred vigorously overnight under an atmosphere of H₂. This mixture was flushed through pressed celite (Et₂O), washed with water (30 mL), and the aq. layer was back-extracted with Et₂O (2 x 10 mL). The combined organic fractions were dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography (10% Et₂O/pentane) gave the steroid **32** (0.7 mg, 9%) as a white powder. ¹H-NMR (CDCl₃, 300 MHz) δ 7.05 (d, J=8.5, 1H), 6.71 (dd, J=8.5, 2.5, 1H), 6.60 (d, J=2.5, 1H), 4.62 (dd, J=9.0, 8.3, 1H), 3.77 (s, 3H), 2.79 (ddd, J=16.6, 4.8, 2.0, 1H), 2.70–2.56 (m, 2H), 2.28–2.14 (m, 1H), 2.09–1.98 (m, 1H), 2.05 (s, 3H), 1.86–1.61 (m, 7H), 1.60–1.45 (m, 3H), 1.42–1.28 (m, 1H), 0.91 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 75 MHz) δ 171.07, 157.32, 137.78, 133.79, 130.21, 113.24, 112.04, 82.65, 55.15, 47.42, 41.71, 41.34, 37.75, 37.56, 31.47, 28.81, 26.96, 22.26, 21.16, 20.89, 13.43 ppm. FTIR (neat) 2929.3, 2848.7, 1736.4, 1609.9, 1499.9, 1464.6, 1446.2, 1372.2, 1241.3, 1153.3, 1035.8, 912.6, 838.6, 818.4, 742.0 cm⁻¹. HRMS (EI) Calculated for C₂₁H₂₈O₃: 328.2038 (M⁺); Found: 328.2023.

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