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Highly Convergent, Stereospecific Synthesis of 11-*cis*-Retinoids by Metal-Catalyzed Cross-Coupling Reactions of (*Z*)-1-Alkenylmetals

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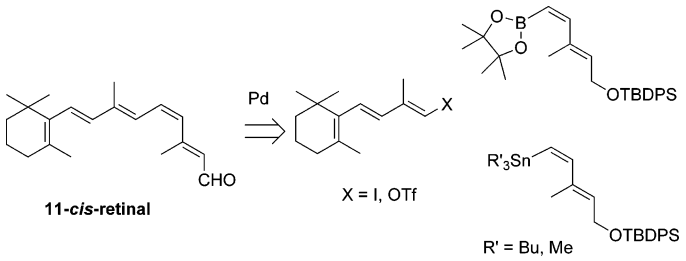

A stereospecific synthesis of 11-*cis*-retinoids has as its key step the hitherto unexplored palladium-catalyzed cross-coupling of *trans*-trienyl electrophiles and (1*Z*,3*E*)-penta-1,3-dienyl boronates (a Suzuki−Miyaura reaction) or stannanes (a Stille reaction). This highly convergent approach constitutes the first application of *cis*-organometallic moieties to the synthesis of 11-*cis*-retinoids and represents a general, straightforward route to the visual chromophore.

Introduction

Vision in vertebrates begins with the photoisomerization of rhodopsin, the light-absorbing pigment present in the photoreceptor cells of the retina. Rhodopsin, an integral membrane protein belonging to the G protein-coupled receptor (GPCR) superfamily, consists of the apoprotein opsin and a covalently linked ligand chromophore, 11-*cis*-retinal (**1**, Scheme 1), which forms a protonated Schiff base with opsin lysine 296. Upon photon absorption, 11-*cis*-retinal is isomerized to the all-*trans* configuration, in less than 200 fs with a quantum yield of 0.65, in one of the fastest and most efficient photochemical reactions in biology. This rearrangement activates the receptor by triggering a conformational change in the protein moiety that sets off a G protein-mediated signal transduction cascade that eventually terminates in a visual nerve impulse.[1]

Clarification of such an extremely complex mechanism requires multidisciplinary collaboration. The significant progress made during the past 20 years has involved a combination of structural, biochemical, biophysical, spectroscopic, recombinant, and computational techniques. In particular, the availability of crystal structures for the dark, inactive[2] and several light-activated photointermediate states[3] of vertebrate visual rhodopsin has provided important mechanistic and energetic insights into the transformations underlying agonist-dependent activation of this and other G-protein-coupled receptors.[4]

Artificial visual pigments, generated by incubation of wild-type or mutant opsin with synthetic analogs of 11-*cis*-retinal, have been of paramount importance in bioorganic studies of rhodopsin and the visual cycle. The use of synthetic retinals with chain or ring structural modifications, photoaffinity labeling analogs and conformationally rigid or 11-*cis*-locked derivatives has provided valuable insights into the structural requirements of the chromophore, its biologically relevant conformation in the rhodopsin binding site, and its movement through the various intermediate stages of the visual transduction path.[5]

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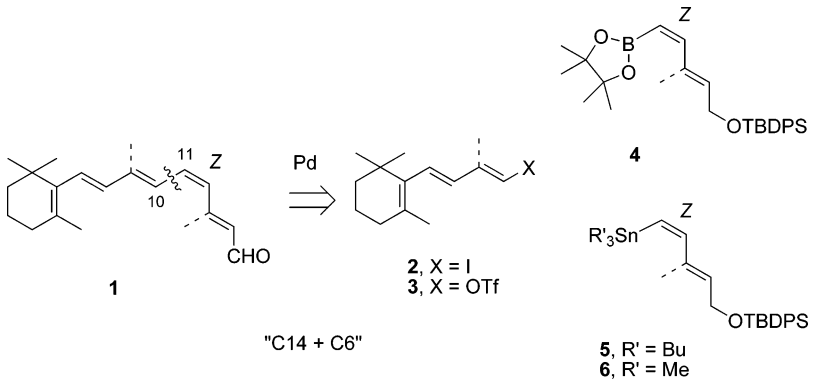
SCHEME 1. Retrosynthetic Analysis



Unfortunately, despite the obvious interest in these analogs, access to 11-*cis*-retinoids has been often complicated by their extreme sensitivity to light and temperature, which results in their isomerization under conditions in which most *Z* double bonds survive. Traditional methods based on sigmatropic rearrangements of an allene precursor, photoisomerization of all-*trans* analogs, hydrogenation of acetylene precursors, or classical olefination reactions (Wittig, Horner−Emmons) have usually resulted in low yields and/or the formation of complex isomeric mixtures.[6]

Recently, substantial synthetic effort toward these metabolites has led to some more efficient approaches. Kobayashi,[7] for example, has employed the highly stereoselective Wittig reaction of an (*E*)-oxidoallylic phosphorane reagent with aldehydes in a "C15 + C5" route to *cis*-retinoids. Lugtenburg[8] has synthesized retinonitriles in quantitative yield, with >60% 11*Z* selectivities, by using Horner−Wadsworth−Emmons reactions with diphenyl phosphonates. Ito[9] has achieved a highly stereoselective synthesis of (11*Z*)-retinal itself and some 9-substituted analogues by employing the Peterson reaction of a β-ionylideneacetaldehyde-tricarbonyliron complex with ethyl trimethylsilylacetate. Nakanishi[10] has reported that semi-hydrogenation of 11-yne retinoid precursors with Cu/Ag-activated Zn dust in methanol/water affords retinols in good yields (>95%) and mainly as the 11-*cis*-isomers (13:1 *Z*/*E* ratio). The same author has also shown that photoisomerization of all-*trans*-3-diazo-4-oxo-retinal (an analog used for photoaffinity labeling) with retinochrome, an isomerase isolated from the visual cells of cephalopods, proceeds smoothly in a catalytical fashion to lead to 11-*cis*-3-diazo-4-oxo-retinal (75% of the isomeric mixture).[11] However, notwithstanding this assorment of synthetic approaches, there is as yet no definitive route to 11-*cis*-retinoids.

Transition-metal-catalyzed cross-coupling processes,[12] the Suzuki[13] and Stille[14] reactions in particular, offer a powerful and general methodology for forming carbon−carbon bonds. In the retinoid field, both reactions have been extensively applied to the *trans*-series.[15] By contrast, to the best of our knowledge, only three applications of cross-coupling reactions to the preparation of 11-*cis*-retinoids have been reported, all of them involving the Suzuki reaction. Uenishi[16] achieved the first strictly stereocontrolled synthesis of (11*Z*)-retinal and (11*Z*)-13-demethylretinal by Suzuki cross-coupling of a *cis*-tetraenyl bromide with trisubstituted alkenyl boronic acids, exploiting the rate-enhancement effect of silver salts. De Lera and López[17] described a highly convergent route to (11*Z*)-9-demethylretinoids based on the thallium-accelerated palladium-catalyzed Suzuki cross-coupling of (*E*)-trienyl boronic acids and a (*Z*)-alkenyl iodide for stereospecific construction of the central $C_{10}-C_{11}$ single bond of the pentaene. More recently, Uneshi[18] has used this same approach in the first synthesis of (11*Z*)-13-aryl substituted retinals. It is worthwhile to note that, in all three

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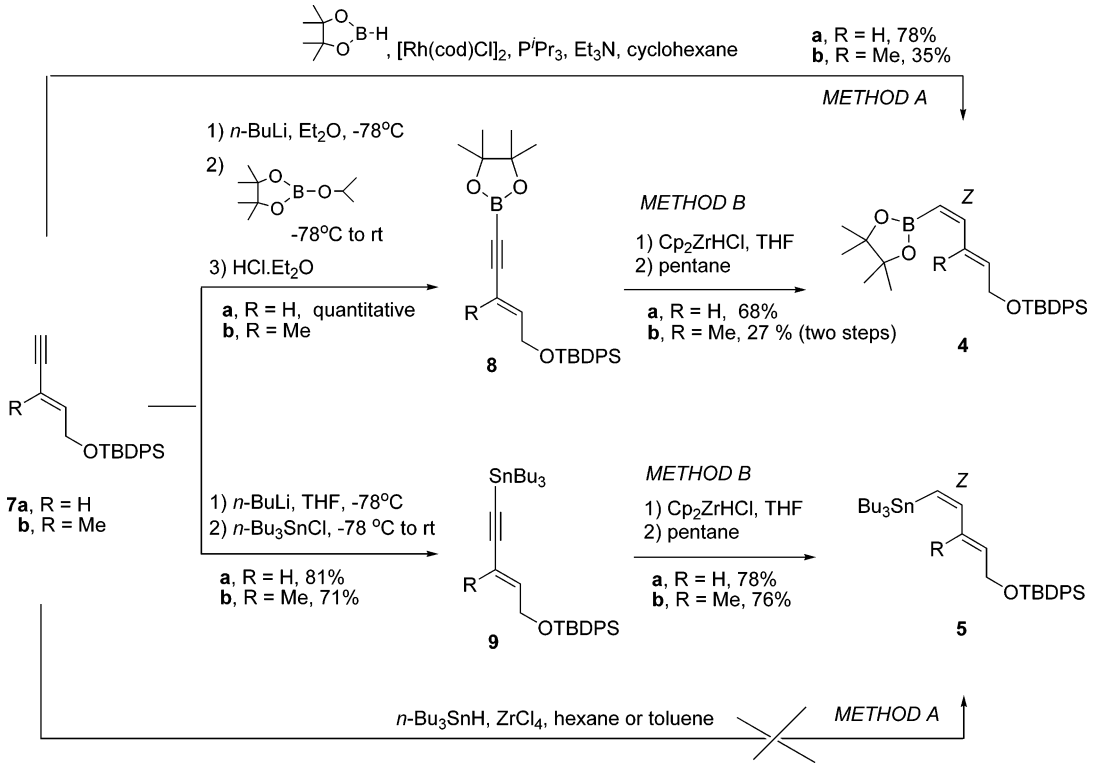
SCHEME 2. Synthesis of (1*Z*,3*E*)-1,3-Dienylmetal Intermediates 4 and 5 from Alkynes 7 (Methods A and B)



cases, the *cis*-moiety is supplied by the electrophilic (halide) coupling partner. As a matter of fact, even though reliable procedures have in recent years been developed for the efficient regio- and stereocontrolled preparation of *cis*-alkenyl metals, there has been no literature precedent related to the use of this type of intermediate in the synthesis of 11-*cis*-retinoids.[19]

As part of our ongoing work on the chemistry and biology of natural and synthetic retinoids,[15b,17,20] we have now developed and describe herein a new stereospecific synthesis of 11-*cis*-retinal and related chain-demethylated retinoids that is based on the hitherto unexplored palladium-catalyzed cross-coupling of *trans*-trienyl electrophiles and (1*Z*,3*E*)-1,3-dienylmetals, either boronates (a Suzuki reaction) or stannanes (a Stille reaction).

Results and Discussion

As in our previous approach to the 11-*cis* series,[17] we aimed for a highly convergent "C14 + C6" strategy that would involve the construction of the central $C_{10}-C_{11}$ single bond as its key step (Scheme 1). The difference would be that the *trans*-moiety would now act as the electrophilic partner, whereas the *cis*-moiety would perform as the alkenyl metal partner.

The electrophilic fragments *trans*-C14 (trienyl iodides **2** and triflate **3**) were readily obtained from β-ionone following well-established synthetic routes.[17] For the *cis*-C6 organometallic intermediates (dienylboronates **4** and stannanes **5** and **6**), four frequently cited methods were evaluated (see Schemes 2 and 3): *trans*-hydrometalation of an enyne precursor (Method A); hydrozirconation of a 1-alkynylmetal followed by hydrolysis (Method B); trapping of a vinylanion with a metallic electrophile (Method C); and palladium-catalyzed cross-coupling of a vinyl halide with a metallic nucleophile (Method D).

Synthesis of Pinacol *cis*-Vinylboronates 4. Method A. *trans*-Hydrometalation: Rhodium-catalyzed formal *trans*-hydroboration of terminal acetylenes. (*Z*)-1-Alkenylboranes cannot be obtained directly by hydroboration because both the uncatalyzed and the metal-catalyzed reactions yield (*E*)-1-alkenylboranes through the *anti*-Markovnikov and *syn*-addition of the borane reagent to the triple bond.[21] However, Miyaura[22] has recently reported a formal *trans*-hydroboration of terminal acetylenes that employs pinacol- or catecholborane in the presence of a Rh(I)-P^{i}Pr$_3$ complex and Et_3N and leads straightforwardly to *cis*-1-alkenylboronates. The use of more than 1 equiv of Et_3N and alkyne in excess of the borane reagent appear to be critical factors to achieve high yield and high *cis*-selectivity.

Prompted by the apparent simplicity of the method, we decided to apply these Miyaura's conditions in our first

(19) A stereocontrolled synthesis of 6-*s*-*cis*- and 6-*s*-*trans*-locked 9*Z*-retinoids by hydroxyl-accelerated Stille coupling of (*Z*)-tri-*n*-butylstannylbut-2-en-1-ol and bicyclic dienyl triflates has been described: (a) Domínguez, B.; Pazos, Y.; de Lera, A. R. *J. Org. Chem.* **2000**, *65*, 5917−5925. Many other examples of stereospecific cross-coupling of (*Z*)- and (*E*)-1-alkenylboronates or stannanes can be found in the literature. For some representative papers, see: (b) He, R.; Deng, M. *Org. Lett.* **2002**, *4*, 2759−2762. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Tsukano, C.; Satake, M.; Sasaki, M. *Chem. Eur. J.* **2004**, *10*, 4894−4909. (c) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2004**, *126*, 11254−11267. (d) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 17111−17117.

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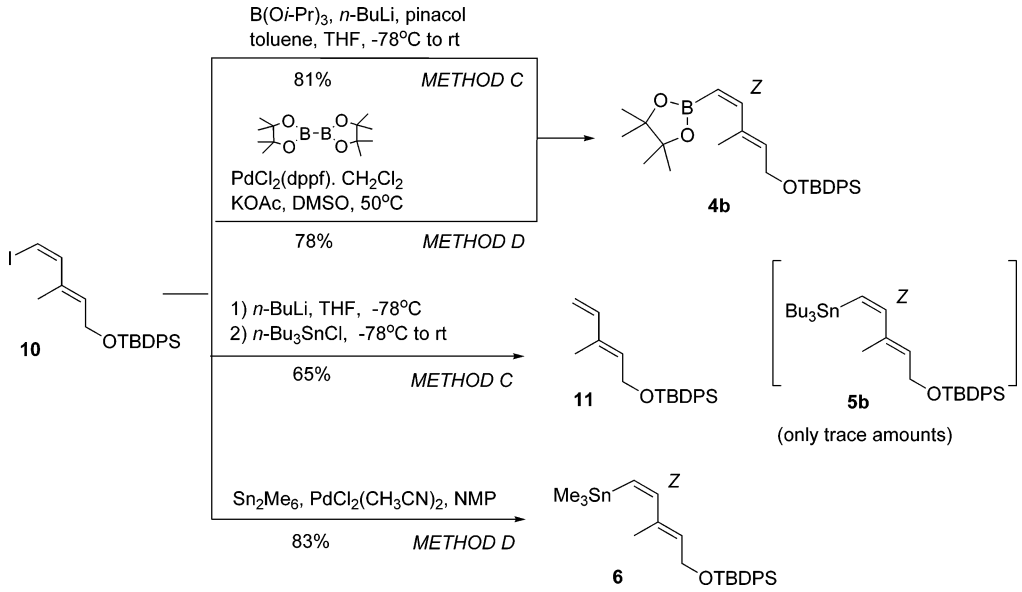
SCHEME 3. Synthesis of (1*Z*,3*E*)-1,3-Dienylmetal Intermediates 4−6 from Iodide 10 (Methods C and D)



approximation to the *cis*-vinylboronates **4**. Thus, pinacolborane was added to a solution of $[Rh(cod)Cl]_2$, P^iPr_3, and Et_3N in cyclohexane, and the mixture was stirred for 30 min at room temperature. An excess of precursor enyne **7** was then added, and stirring was continued for 4 h. The reaction with **7a** proceeded smoothly, affording dienylboronate **4a**[23] in 78% yield. By contrast, enyne **7b**[24] was converted to boronate **4b** in only a modest 35% yield; most of the product mixture was starting material, even when longer reaction times and/or additional equivalents of catalyst and amine were employed.

Method B. Hydrozirconation of 1-alkynylmetals. It is well-established that (*Z*)-1-alkenylmetals can be obtained from alkynylmetallic precursors, in one pot, by reaction with zirconocene hydrochloride [Schwartz's reagent, $Cp_2Zr(H)Cl$][25] in THF followed by treatment with excess H_2O. The hydrozirconation proceeds by *syn*-addition to give essentially pure (*E*)-1,1-bimetalloalkenes, and because the $C(sp^2)$-Zr bond is usually more reactive than the other C-M bond with electrophiles, the hydrolysis occurs mainly at the former, with retention of configuration. Srebnik[26] has applied this methodology to the synthesis of a variety of functionalized *cis*-alkenylboronates.

In the present work, the precursor required for **4a**, 1-alkynyldioxaborolane **8a**, was readily obtained in quantitative yield by reaction of the 1-lithioalkyne derivative of **7a** with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, followed by addition of ethereal hydrogen chloride. Subsequent hydrozirconation of **8a** with 1.2 equiv of zirconocene hydrochloride afforded, after addition of pentane and purification, a 68% yield of the desired *cis*-vinyl boronate **4a**. Disappointingly, however, all attempts to prepare 1-alkynylboronate **8b** from **7b** led to an inseparable mixture of the desired product and starting material in an approximately 5:1 molar ratio, as measured by ^1H NMR. When this mixture was reacted with $Cp_2Zr(H)Cl$ under the conditions described above, *cis*-vinyl boronate **4b** could only be obtained, after chromatographic separation, in a poor 27% overall yield.

Method C. Trapping of vinylanions with metallic electrophiles. In light of the numerous difficulties found in the synthesis of **4b** from enyne **7b**, we decided to try alternative methods starting from precursor iodide **10**.[17] Pleasingly, application of the experimental conditions described by Lautens,[27] which involved treatment of a cooled (−78 °C) solution of iodide **10** and tri-isopropylborate in THF/toluene with *n*-BuLi for 30 min, followed by the addition of pinacol, cleanly afforded the target boronate **4b** in a satisfactory 81% yield after 2 h of reaction.

Method D. Palladium-catalyzed cross-coupling with nucleophilic metallic species. Miyaura has recently reported that palladium-catalyzed borylation of 1-alkenyl electrophiles (halides or triflates) with tetra(alkoxo)diboranes, in the presence of a base, affords stereospecific access to vinyl boronates.[28]

In our case, heating a solution of iodide **10** and bis-(pinacolato)diborane in DMSO with $PdCl_2(dppf)$-CH_2Cl_2 and AcOK, at 50 °C for 4 h, gave boronate **4b** in 78% yield.

Synthesis of *cis*-Vinylstannanes 5 and 6. Method A. *trans*-Hydrometalation: Lewis acid catalyzed *trans*-hydrostannation of terminal acetylenes. Alkenylstannanes can be synthesized by hydrostannation of alkynes by using either radical initiators or transition metal catalysts; however, the radical-induced procedure often exhibits poor stereoselectivity, and the transition-metal-catalyzed reaction usually leads to a mixture of the two possible regioisomers.[29] Notably, Yamamoto[30] has recently reported that the hydrostannation process is catalyzed dramatically by a Lewis acid such as $ZrCl_4$ to produce

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cis-vinylstannanes by a regio- and stereoselective *anti*-hydrostannation. Although details of the mechanism are still unknown, the coordination of the triple bond to the Lewis acid has been proposed as a key step.

Because this procedure constitutes the most direct approach to *cis*-vinylstannanes, we chose it for our first approximation to (1*Z*,3*E*)-1,3-dienylstannanes **5**. Unfortunately, however, treatment of enynes **7** with *n*-Bu_3SnH and 0.2 equiv of $ZrCl_4$, in hexane or toluene, gave only trace amounts of the desired products **5**, most of the starting material being recovered even after reaction times of up to12 h.

Method B. Hydrozirconation of 1-alkynylmetals. In the same way as we have previously discussed for *cis*-vinylboronates, reaction of tin acetylenes with $Cp_2Zr(H)Cl$, followed by a proton quenching, stereoselectively affords (*Z*)-vinylstannanes in high yields. Lipshutz[31] was a pioneer in the use of this methodology.

In our case, the required tin acetylenes **9**[32] were uneventfully synthesized from enynes **7a** and **7b** (in 81% and 71% yield, respectively) by trapping of the corresponding alkynyllithiums with tributyltin chloride. Subsequent treatment of compounds **9** with $Cp_2Zr(H)Cl$ afforded the dienylstannanes **5a**[33] and **5b** in, respectively, 78% and 76% yield.

Method C. Trapping of vinylanions with metallic electrophiles. Despite numerous reports of the successful use of this methodology to synthesize *cis*-vinylstannanes,[34] it failed to afford (1*Z*,3*E*)-dienylstannane **5b**. Unexpectedly, lithium−halogen exchange in vinyl iodide **10**, followed by treatment with tributyltin chloride, provided **5b** in only trace amounts, the major product being a 65% yield of the terminal alkene **11**.[35] All attempts to improve this result (longer reaction times, higher temperatures, larger amounts of electrophile, use of trimethyltin chloride, etc.) were fruitless.

Method D. Palladium-catalyzed cross-coupling with nucleophilic metallic species. Farina[36] has reported that treatment of a solution of a vinyl halide in NMP with hexamethylditin and a catalytic amount of an homogeneous palladium catalyst affords the trimethyl vinylstannane in good yield with complete retention of stereochemistry. The reaction does not work, however, when hexabutylditin is used instead.

Application of this method to iodide **10**, by treatment with Sn_2Me_6 and $PdCl_2(CH_3CN)_2$ in NMP, afforded the new (1*Z*,3*E*)-dienyl trimethylstannane **6** in 83% yield.

Synthesis of (1*Z*,3*E*)-1,3-Dienylmetals: Summary, Work-up, and Characterization. All the required isomerically pure *cis*-vinylmetallic intermediates were obtained in good yield by one or another of the four methods considered. Dienylboronate **4a** was easily prepared from enyne **7a** by either Method A or Method B. These methods failed to afford its methylated analog **4b**, which was alternatively obtained from iodide **10** by either Method C or Method D. Neither **5a** nor **5b** could be prepared by Method A, and nor was **5b** obtainable by Method C, but Method B afforded good yields of both tributyl dienylstannanes. Finally, Method D gave the trimethyl analog **6** in an excellent yield.

Pinacol boronates **4** are stable compounds that were handled and purified without trouble. However, stannanes **5** and **6** are acid-sensitive compounds that undergo almost complete protodestannylation on silicagel, and therefore they had to be purified by flash chromatography on neutral alumina.

The stereochemistry of the (1*Z*,3*E*)-1,3-dienyl metallic species was unequivocally established by ^1H NMR and ^{13}C NMR spectra analysis.[37] In the case of the vinylboronates, the room temperature ^{13}C spectra failed to show a signal for the carbon that is bonded directly to the quadrupolar boron, presumably because the signal was broadened by incomplete averaging of the scalar coupling and lost under the noise, but the expected signal could be observed when the spectra were run at low temperature (253 K).[38]

Synthesis of 11-*cis*-Retinyl Ethers 12−15: Suzuki−Miyaura and Stille Cross-Coupling Steps. Having successfully prepared electrophiles **2** and **3** and the boron and tin species **4**−**6**, we proceeded to couple them. Selected results for the Suzuki and Stille approaches to 11-*cis*-retinyl ether **15** and its 9- and/or 13-demethylated analogs **12**−**14** are shown in Schemes 4−6. A full account of experimental conditions and yields is given in Table 1 (Suzuki−Miyaura couplings) and Table 2 (Stille couplings).

Suzuki−Miyaura Cross-Coupling Reactions. Since the Suzuki reaction is more tolerant than the Stille coupling to steric hindrance between the coupling partners,[13] we first focused on the coupling of vinylboronates **4**.

To couple **4** with iodides **2**, we used the thallium-accelerated version of the Suzuki coupling developed by Kishi [$Pd(Ph_3P)_4$, TlOH (aq), THF, rt],[39] which had already given good results in our previous approach to *cis*-retinoids.[17] As expected, the reaction proceeded readily in all cases (3−5 h, rt), giving 11-*cis*-retinyl ethers **12**−**15** in 74%, 90%, 80%, and 73% yield, respectively (Schemes 4−6). A slightly lower yield was obtained when the more convenient TlOEt[40] was used as the base (60% for **15**; Table 1), whereas when triflate **3** was employed as the electrophile and K_3PO_4 as the base, the yield of **14** fell (63%, Scheme 5) but that of **15** rose slightly (76%, Scheme 6).

Stille Cross-Coupling Reactions. The Stille cross-coupling reactions were first carried out under ligand-free conditions [$PdCl_2(CH_3CN)_2$, DMF, rt].[41] The coupling of **2a** proceeded uneventfully with both **5a** and **5b**, affording retinyl ethers **12** and **13** in good yields (7 h, 70% and 83%, respectively; Scheme 4). However, the more hindered iodide **2b** reacted more sluggishly (the reactions with **5** were only half completed after 6 h) and gave substantially lower yields (57% and 50% for **14**

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(38) Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; John Wiley & Sons: New York, 1988.

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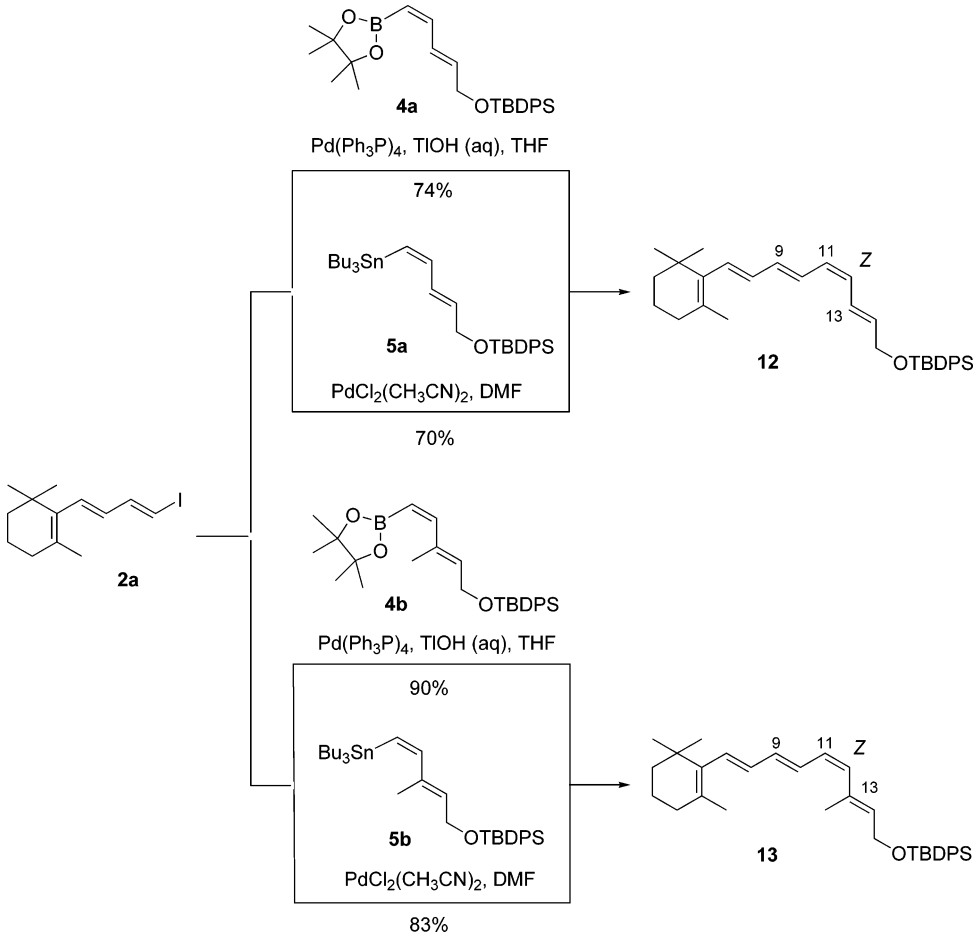
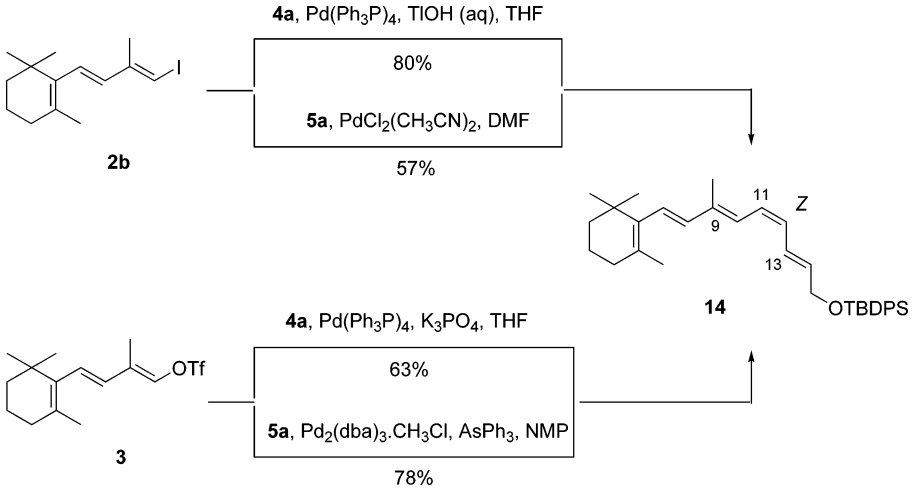
(41) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817. (b) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221−2224.

SCHEME 4. Synthesis of 11-*cis*-9,13-Demethyl and 11-*cis*-9-Demethyl Retinyl Ethers 12 and 13



SCHEME 5. Synthesis of 11-*cis*-13-Demethyl Retinyl Ether 14



and **15**, respectively; Table 2) even when the more reactive trimethylvinyl stannane **6** was employed (44% for **15**; Table 2).

In order to improve these yields, the coupling of iodide **2b** with trimethyl stannane **6** was investigated under conditions specifically recommended for sterically congested fragments. Gratifyingly, application of the protocol used by Corey[42] for coupling sterically encumbered 1-substituted vinylstannanes [Pd(PPh$_3$)$_4$, LiCl, CuCl, DMSO] significantly enhanced the reaction, providing retinyl ether **15** in a good yield (3 h, 69%; Table 2). Even better results were achieved when the recently reported Baldwin's variant[43] of the Stille reaction was used. These conditions [Pd(Ph$_3$P)$_4$, CsF, CuI, DMF], which exploit synergy between copper(I) salts and the fluoride ion, proved to be the

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SCHEME 6. Synthesis of 11-*cis*-Retinyl Ether 15 and 11-*cis*-Retinal (1)

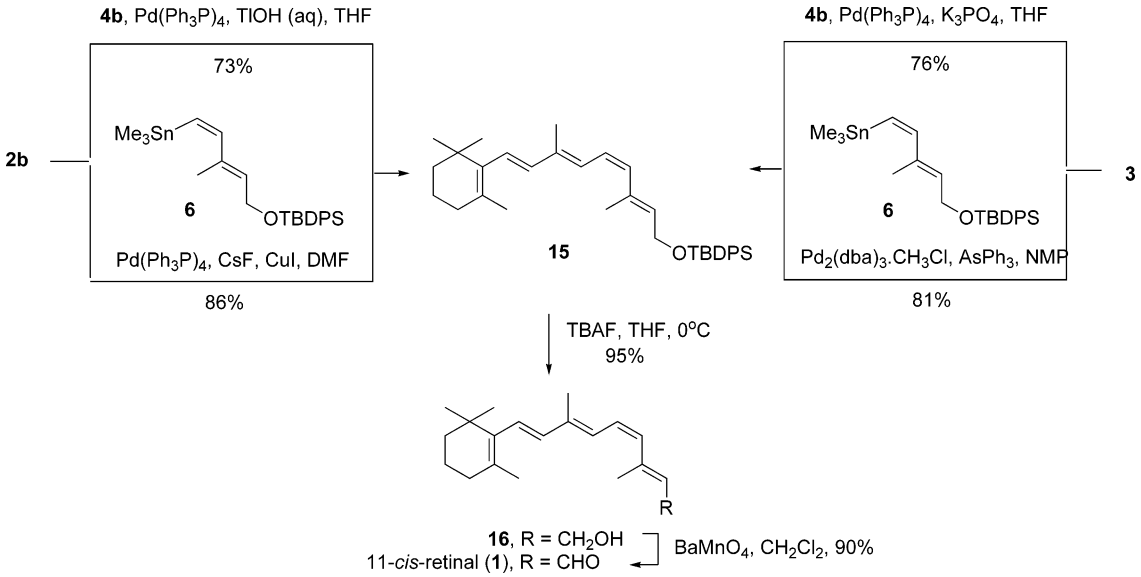

TABLE 1. Summary of Suzuki−Miyaura Cross-Coupling Reactions

electrophile	boronate	reaction conditions	retinyl ether (% yield)
2a	**4a**	$Pd(PPh_3)_4$, TlOH (aq), THF	**12** (74)
2a	**4b**	$Pd(PPh_3)_4$, TlOH (aq), THF	**13** (90)
2b	**4a**	$Pd(PPh_3)_4$, TlOH (aq), THF	**14** (80)
3	**4a**	$Pd(PPh_3)_4$, K_3PO_4, THF	**14** (63)
2b	**4b**	$Pd(PPh_3)_4$, TlOH (aq), THF	**15** (73)
2b	**4b**	$Pd(PPh_3)_4$, TlOEt, THF	**15** (60)
3	**4b**	$Pd(PPh_3)_4$, K_3PO_4, THF	**15** (76)

TABLE 2. Summary of Stille Cross-Coupling Reactions

electrophile	stannane	reaction conditions	retinyl ether (%) yield)
2a	**5a**	$PdCl_2(CH_3CN)_2$, DMF	**12** (70)
2a	**5b**	$PdCl_2(CH_3CN)_2$, DMF	**13** (83)
2b	**5a**	$PdCl_2(CH_3CN)_2$, DMF	**14** (57)
3	**5a**	$Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, NMP	**14** (78)
2b	**5b**	$PdCl_2(CH_3CN)_2$, DMF	**15** (50)
2b	**6**	$PdCl_2(CH_3CN)_2$, DMF	**15** (44)
2b	**6**	$Pd(PPh_3)_4$, LiCl, CuCl, DMSO	**15** (69)
2b	**6**	$Pd(PPh_3)_4$, CsF, CuI, DMF	**15** (86)
3	**6**	$Pd_2(dba)_3.CHCl_3$, $AsPh_3$, NMP	**15** (81)

most efficient ones, delivering **15** in an excellent 86% yield after 3 h at room temperature (Scheme 6).

To couple vinyltriflate **3** to stannanes **5a** and **6**, we used the conditions developed by Farina,[44] which employ the "soft" palladium catalyst $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$ as ligand, and NMP as solvent. The reaction proceeded smoothly in both cases to give retinyl ethers **14** and **15** in 78% and 81% yield, respectively (Schemes 5 and 6). In contrast to other reports, LiCl was not necessary.

Finally, in order to complete the total synthesis of 11-*cis*-retinal (**1**), retinyl ether **15** was reacted in a sequence that entailed deprotection [TBAF, THF, 0 °C, 95% yield] to give 11-*cis*-retinol **16** and subsequent oxidation [$BaMnO_4$, CH_2Cl_2, 90% yield] to afford the target visual chromophore as an isomerically pure compound (Scheme 6).[45]

Conclusion

A new approach to 11-*cis*-retinoids has been developed in which the key step is the hitherto unexplored palladium-catalyzed cross-coupling of a *trans*-trienyl electrophile (an iodide or triflate derived from β-ionone) with (1*Z*,3*E*)-penta-1,3-dienyl boronates (the Suzuki−Miyaura reaction) or stannanes (the Stille reaction). The required *cis*-vinyl metallic species were obtained in good yield by known procedures starting from alkyne or iodide precursors. In all cases, the key cross-coupling step proceeded very smoothly, with no isomerization of the 11*Z* double bonds, to afford geometrically pure retinoids in good yields. This highly convergent approach constitutes a general, straightforward route to these unstable polyenes and could be used to prepare a wide range of analogs of the visual chromophore.

Experimental Section

2-[(*E*)-5′-(*tert*-Butyldiphenylsilyloxy)pent-3′-en-1′-yn-1′-yl]-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (8a). To a solution of (*E*)-5-*tert*-butyldiphenylsilyloxypent-3-en-1-yne (**7a**; 500 mg, 1.50 mmol) in Et_2O (2 mL), cooled to −78 °C, was added *n*-BuLi (2.5 M in hexanes, 0.72 mL, 1.80 mmol). The mixture was stirred for 30 min, stood at room temperature for 30 min, cooled again to −78 °C, and then treated with a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.4 mL, 1.80 mmol) in Et_2O (5 mL). After 1 h at −78 °C and 3 h at room temperature, this mixture was treated with $HCl{\cdot}Et_2O$ (2.0 M, 0.9 mL, 1.80 mmol, slow addition), stirred for 20 min, filtered through Celite, and concentrated under reduced pressure for 8 h at 40 °C, affording **8a** as a yellow oil (690 mg, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.29 (s, 12H), 4.25 (dd, J = 3.8, 2.2 Hz, 2H), 5.99 (dt, J = 15.8 Hz, 2.2 Hz, 1H), 6.38 (dt, J = 15.8, 3.8 Hz, 1H), 7.2−7.4 (m, 6H), 7.5−7.7 (m, 4H) ppm. ^{13}C NMR (75 MHz,

(44) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(45) Compounds **13**, **14**, and **15** having a ^{t}BuMe$_2$Si group in place of a ^{t}BuPh$_2$Si group are known: see ref 17 for **13** and ref 16 for **14** and **15**. Reactions and purification of the final products were carried out in the absence of light. Purification of the acid-sensitive *cis*-retinoids was carried out by flash chromatography using neutral alumina as the adsorbent.

$CDCl_3$) δ 19.3 (C), 24.7 (4xCH_3), 26.7 (3 × CH_3), 63.4 (CH_2), 83.2 (2 × C), 84.3 (C), 107.8 (CH), 127.7 (4 × CH), 129.8 (2 × CH), 133.1 (2xC), 134.9 (C), 135.4 (4 × CH), 145.8 (CH) ppm. MS (CI) *m*/*z* (%) 447 (M^+ + H, 32), 369 (25), 101 (100). HRMS (CI) calcd for $C_{27}H_{36}BO_3Si$, 447.2527; found, 447.2526.

(*E*)-5-*tert*-Butyldiphenylsilyloxy-1-tributylstannylpent-3-en-1-yne (9a). *n*-BuLi (1.6 M in hexanes, 9.3 mL, 14.85 mmol) was added to a solution of alkyne **7a** (4.3 g, 13.5 mmol) in THF (55 mL) at −78 °C, and the reaction mixture was stirred for 30 min at −78 °C and 30 min at 0 °C, cooled to −78 °C, treated with *n*-Bu_3SnCl (4.0 mL, 14.85 mmol), and allowed to warm to room temperature over 5 h. The solvent was removed under vacuum, and the residue was partitioned between diethyl ether (30 mL) and H_2O (3 × 30 mL). The ethereal layer was washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the crude (Al_2O_3, hexane) afforded **9a**[32] as a colorless oil (6.7 g, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 9H), 1.0−1.1 (m, 6H), 1.10 (s, 9H), 1.3−1.4 (m, 6H), 1.5−1.7 (m, 6H), 4.25 (dd, J = 4.0, 2.1 Hz, 2H), 5.99 (dt, J = 15.7, 2.1 Hz, 1H), 6.21 (dt, J = 15.7 Hz, 4.0 Hz, 1H), 7.2−7.4 (m, 6H), 7.5−7.7 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2 (3 × CH_2, $^1J_{Sn-C}$ = 373.6 Hz), 13.8 (3 × CH_3), 19.3 (C), 26.8 (3 × CH_3), 27.1 (3 × CH_2), 28.9 (3 × CH_2,), 63.6 (CH_2), 93.6 (C), 108.3 (C), 109.4 (CH), 127.5 (4 × CH), 129.8 (2 × CH), 133.0 (2 × C), 135.3 (4 × CH), 141.6 (CH) ppm. MS (CI) *m*/*z* (%) 610 (4), 553 (52), 529 (100). HRMS (CI) calcd for $C_{33}H_{50}$OSiSn, 610.2653; found, 610.2663.

(*E*)-5-*tert*-Butyldiphenylsilyloxy-3-methyl-1-tributylstannylpent-3-en-1-yne (9b). Following the same procedure as described for compound **9a**, treatment of a solution of (*E*)-5-*tert*-butyldiphenylsilyloxy-3-methylpent-3-en-1-yne (**7b**; 3.41 g, 10.7 mmol) in THF (45 mL) with *n*-BuLi (1.6 M in hexanes, 7.3 mL, 11.7 mmol) and *n*-Bu_3SnCl (3.2 mL, 11.7 mmol) afforded **9b** (4.5 g, 71%) as a dark yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 9H), 1.10 (s, 9H), 1.0−1.1 (m, 6H), 1.3−1.4 (m, 6H), 1.6−1.7 (m, 6H), 1.68 (s, 3H), 4.32 (d, J = 6.2 Hz, 2H), 6.05 (t, J = 6.2 Hz, 1H), 7.3−7.5 (m, 6H), 7.6−7.7 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1 (3 × CH_2, $^1J_{Sn-C}$ = 374.0 Hz), 13.7 (3 × CH_3), 17.9 (CH_3), 19.1 (C), 26.7 (3 × CH_3), 26.9 (3 × CH_2), 28.9 (3 × CH_2), 60.8 (CH_2), 90.1 (C), 112.9 (C), 119.5 (C), 127.6 (4 × CH), 129.7 (2 × CH), 133.6 (2 × C), 135.1 (4 × CH), 136.1 (CH) ppm. MS (CI) *m*/*z* (%) 567 (M^+ − Bu, 6), 199 (45), 57 (100). HRMS (CI) calcd for $C_{30}H_{43}$OSiSn, 567.2105; found, 567.2113.

2-[(1′*Z*,3′*E*)-5′-(*tert*-Butyldiphenylsilyloxy)-penta-1′,3′-dien-1′-yl]-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (4a). Method A. Pinacolborane (145 μL, 1.0 mmol) was added to a solution of [Rh(cod)Cl]$_2$ (7.4 mg, 0.015 mmol), ^{i}Pr$_3$P (1.5 μL, 0.06 mmol), and Et_3N (693 μL, 5.0 mmol) in cyclohexane (3 mL) at room temperature. After 30 min, a solution of alkyne **7a** (384 mg, 1.2 mmol) in cyclohexane (1 mL) was added, and the reaction mixture was stirred for 4 h. The solvent was removed under vacuum, and the residue was purified by flash chromatography (SiO_2, 95:5 hexane/AcOEt), affording **4a** as a yellow oil (349 mg, 78% yield). **Method B.** To a stirring suspension of $Cp_2Zr(H)Cl$[25] (144 mg, 0.56 mmol) in THF (6 mL) was added dropwise a solution of pinacol alkynylboronate **8a** (100 mg, 0.22 mmol) in THF (6 mL), and the mixture was stirred for 4 h until hydrozirconation was complete, as evidenced by the disappearance of the insoluble hydride and the formation of a clear solution. It was then diluted with *n*-pentane (20 mL), stirred for a further 20 min, filtered through a short pad of neutral alumina, and concentrated. Flash chromatography of the crude (SiO_2, 95:5 hexane/AcOEt) afforded 68 mg (68% yield) of **4a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.25 (s, 12H), 4.29 (d, J = 4.2 Hz, 2H), 5.36 (d, J = 13.4 Hz, 1H), 5.88 (dt, J = 15.2, 4.2 Hz, 1H), 6.89 (dd, J = 13.4, 11.2 Hz, 1H), 7.27 (dd, J = 11.2, 15.2 Hz, 1H), 7.3−7.5 (m, 6H), 7.6−7.8 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C), 24.8 (4 × CH_3), 26.9 (3 × CH_3), 63.6 (CH_2), 83.0 (2 × C), 118.4 (CH), 127.6 (4 × CH), 129.2 (CH), 129.5 (2 × CH), 133.4 (2 × C), 135.5 (4 × CH), 137.2 (CH), 150.2 (CH) ppm. MS (CI) *m*/*z* (%) 448 (6), 391 (30), 405 (53), 371 (20), 193 (100). HRMS (CI) calcd for $C_{27}H_{37}BO_3Si$, 448.2605; found, 448.2602.

2-[(1′*Z*,3′*E*)-5′-(*tert*-Butyldiphenylsilyloxy)-3′-methylpenta-1′,3′-dien-1′-yl]-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (4b). Method A. Following the same procedure as described for compound **4a**, reaction of [Rh(cod)Cl]$_2$ (7.4 mg, 0.015 mmol), ^{i}Pr$_3$P (1.5 μL, 0.06 mmol), Et_3N (693 μL, 5.0 mmol), pinacolborane (145 μL, 1.0 mmol), and alkyne **7b** (401 mg, 1.2 mmol) in cyclohexane (4 mL) afforded **4b** as a yellow oil (161 mg, 35% yield). **Method B.** Following the same procedure as described for compound **4a**, reaction of alkyne **7b** (161 mg, 0.48 mmol) with *n*-BuLi (2.5 M in hexanes, 0.23 mL, 0.58 mmol) and pinacolborane (0.18 mL, 0.62 mmol) in Et_2O (7 mL) afforded, after treatment with HCl·Et_2O (2.0 M, 0.51 mL, 1.024 mmol) for 20 min and filtration through a short pad of Celite, a mixture of the desired alkynyl boronate **8b** and alkyne **7b**, from which **8b** could not easily be separated. Without further purification, this mixture was dissolved in THF (1.2 mL) and added dropwise via cannula to a suspension of $Cp_2Zr(H)Cl$ (248 mg, 0.96 mmol) in THF (10 mL). The resulting mixture was stirred for 4 h at room temperature, the solvent was removed under vacuum, and hexane (5 mL) was added. This mixture was filtered through a short pad of Celite and concentrated, and the crude was purified by flash chromatography (SiO_2, 95:5 hexane/AcOEt), yielding 60 mg of **4b** (27% overall yield for the two steps). **Method C.** *n*-BuLi (2.5 M in hexanes, 96 μL, 0.24 mmol) was added to a solution of (1*Z*,3*E*)-5-*tert*-butyldiphenylsilyloxy-1-iodo-3-methylpenta-1,3-diene (**10**; 100 mg, 0.21 mmol) and tri-isopropylborate (55 μL, 0.24 mmol) in 3 mL of toluene and 1 mL of THF at −78 °C. After stirring for 30 min, pinacol (28 mg, 0.24 mmol) was added and the reaction mixture was stood at room temperature for 2 h, diluted with Et_2O, and washed with saturated aqueous ammonium chloride solution, water, and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo, and the crude was purified by flash chromatography (SiO_2, 95:5 hexane/AcOEt), yielding 81 mg (81% yield) of **4b**. **Method D.** To a suspension of $PdCl_2$(dppf)·CH_2Cl_2 (5.0 mg, 0.006 mmol), bis(pinacolato)diboron (164 mg, 0.65 mmol), and KOAc (63 mg, 0.65 mmol) in DMSO (2 mL) was added a solution of dienyl iodide **10** (100 mg, 0.22 mmol) in DMSO (1 mL), and the resulting mixture was heated at 50 °C for 4 h, treated with water (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the crude (SiO_2, 89:10:1 hexane/EtOAc/Et_3N) afforded 78 mg (78% yield) of **4b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.26 (s, 12H), 1.68 (s, 3H), 4.32 (d, J = 6.0 Hz, 2H), 5.29 (d, J = 14.8 Hz, 1H), 5.77 (t, J = 6.0 Hz, 1H), 6.69 (d, J = 14.8 Hz, 1H) 7.2−7.4 (m, 6H), 7.5−7.7 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (CH_3), 19.1 (C), 24.8 (4 × CH_3), 26.8 (3 × CH_3), 61.3 (CH_2), 83.4 (2 × C), 116.0 (CH), 127.6 (4 × CH), 129.5 (2 × CH), 133.6 (2 × C), 133.7 (CH), 135.5 (4 × CH), 135.7 (C), 150.3 (CH) ppm. MS (CI) *m*/*z* (%) 463 (M^+ + H, 21), 462 (12), 405 (53), 385 (4), 308 (2), 199 (100). HRMS (CI) calcd for $C_{28}H_{40}BO_3Si$, 463.2839; found, 463.2839.

(1*Z*,3*E*)-5-*tert*-Butyldiphenylsilyloxy-1-tributylstannylpenta-1,3-diene (5a).[33] **Method B.** Following the same procedure as described for compound **4a**, reaction of $Cp_2Zr(H)Cl$ (1.0 g, 4.0 mmol) and alkynylstannane **9a** (1.0 g, 1.63 mmol) in THF (5 mL) for 3 h afforded, after purification by column chromatography (Al_2O_3, hexane), 777 mg (78%) of **5a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 0.9−1.0 (m, 6H), 1.11 (s, 9H), 1.2−1.4 (m, 6H), 1.4−1.6 (m, 6H), 4.29 (d, J = 4.3 Hz, 2H), 5.81 (dt, J = 14.9, 4.3 Hz, 1H), 6.06 (d, J = 12.6 Hz, $^2J_{Sn-H}$ = 60.3 Hz, 1H), 6.35 (dd, J = 14.9 Hz, 10.6 Hz, 1H), 7.11 (dd, J = 12.6, 10.6 Hz, $^3J_{Sn-Htrans}$ = 130.8 Hz, 1H), 7.3−7.5 (m, 6H), 7.6−7.8 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5 (3 × CH_2, $^1J_{Sn-C}$ = 332.8 Hz), 13.8 (3 × CH_3), 19.4 (C), 26.9 (3 ×

CH_3), 27.3 (3 × CH_2), 29.3 (3 × CH_2), 63.9 (CH_2), 127.6 (4 × CH), 129.5 (2 × CH), 131.5 (CH), 133.0 (CH), 133.4 (2 × C), 134.0 (CH), 135.5 (4 × CH), 146.0 (CH) ppm. MS (CI) *m*/*z* (%) 555 (M^+ − Bu, 100), 199 (13). HRMS (CI) calcd for $C_{29}H_{43}OSiSn$, 555.2105; found, 555.2101.

(1*Z*,3*E*)-5-*tert*-Butyldiphenylsilyloxy-3-methyl-1-tributylstannylpenta-1,3-diene (5b). Method B. Following the same procedure as described for compound **4a**, reaction of Cp_2ZrHCl (1.90 g, 7.20 mmol) and alkynylstannane **9b** (1.96 g, 3.13 mmol) in THF (185 mL) for 4 h, followed by addition of *n*-pentane (40 mL), afforded 1.50 g (76%) of **5b** as a colorless oil. **Method C.** *n*-BuLi (1.6 M in hexanes, 462 μL, 0.74 mmol) was added dropwise to a solution of dienyl iodide **10** (200 mg, 0.43 mmol) in THF (4 mL) at −78 °C. After stirring for 1 h at this temperature, *n*-Bu_3SnCl (162 μL, 0.6 mmol) was added, and the solution was allowed to warm to room temperature over 4 h before being filtered through a short pad of neutral alumina. The solvents were removed under vacuum, and the crude was purified by flash chromatography (Al_2O_3, hexane), affording 97 mg (65% yield) of (*E*)-5-(*tert*-butyldiphenylsilyloxy)-3-methylpenta-1,3-diene (**11**)[35] and only trace amounts of **5b**. Spectroscopic data for compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8−1.0 (m, 15H), 1.10 (s, 9H), 1.2−1.4 (m, 6H), 1.4−1.5 (m, 6H), 1.61 (s, 3H), 4.32 (d, J = 5.9 Hz, 2H), 5.70 (t, J = 5.9 Hz, 1H), 5.83 (d, J = 13.4 Hz, $^2J_{Sn-H}$ = 56.7 Hz, 1H), 7.01 (d, J = 13.4 Hz, $^3J_{Sn-Htrans}$ = 136.4 Hz, 1H), 7.3−7.5 (m, 6H), 7.7−7.8 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4 (3 × CH_2, $^1J_{Sn-C}$ = 336.2 Hz), 13.8 (3 × CH_3), 15.4 (CH_3), 19.3 (C), 26.9 (3 × CH_3), 27.4 (3 × CH_2), 29.3 (3 × CH_2), 61.4 (CH_2), 127.5 (4 × CH), 128.4 (CH), 128.5 (CH), 129.5 (2 × CH), 133.6 (2 × C), 135.6 (4 × CH), 137.7 (C), 150.6 (CH) ppm. MS (CI) *m*/*z* (%) 569 (M^+ − Bu, 13), 512 (5), 199 (65), 57 (100). HRMS (CI) calcd for $C_{30}H_{45}OSiSn$, 569.2280; found, 569.2280. Spectroscopic data for compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.64 (s, 3H), 4.43 (d, J = 5.9 Hz, 2H), 5.05 (d, J = 10.4 Hz, 1H), 5.17 (d, J = 17.4 Hz, 1H), 5.74 (t, J = 5.9 Hz, 1H), 6.44 (dd, J = 10.4, 17.4 Hz, 1H), 7.3−7.5 (m, 6H), 7.6−7.8 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (CH_3), 19.3 (C), 27.0 (3 × CH_3), 61.2 (CH_2), 112.2 (CH_2), 127.6 (4 × CH), 129.5 (2 × CH) 131.5 (CH), 133.6 (2 × C), 134.3 (C), 135.5 (4 × CH), 140.8 (CH) ppm. MS (CI) *m*/*z* (%) 337 (M^+ + H, 2), 279 (10), 259 (12), 29 (100). HRMS (CI) calcd for $C_{22}H_{29}OSi$, 337.1988; found, 337.1991.

(1*Z*,3*E*)-5-*tert*-Butyldiphenylsilyloxy-3-methyl-1-trimethylstannylpenta-1,3-diene (6). Method D. To a solution of trienyl iodide **10** (100 mg, 0.22 mmol) in NMP (2 mL) were added $PdCl_2(CH_3CN)_2$ (6 mg, 0.022 mmol) and hexamethyl distannane (100 μL, 0.49 mmol). The mixture was stirred for 3 h at room temperature and filtered through a short pad of neutral alumina (hexane), the solvent was removed under vacuum, and the crude was purified by flash chromatography (Al_2O_3, hexane), yielding 90 mg (83% yield) of **6** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, $^2J_{Sn-H}$ = 54.2 Hz, 9H), 1.05 (s, 9H), 1.56 (s, 3H), 4.27 (d, J = 5.9 Hz, 2H), 5.66 (t, J = 5.9 Hz, 1H), 5.83 (d, J = 13.4 Hz, $^2J_{Sn-H}$ = 66.8 Hz, 1H), 6.94 (d, J = 13.4 Hz, $^3J_{Sn-H\ trans}$ = 150.2 Hz, 1H), 7.3−7.5 (m, 6H), 7.6−7.8 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −7.4 (3 × CH_3), 15.6 (CH_3), 19.6 (C), 26.8 (3 × CH_3), 61.1 (CH_2), 127.6 (4 × CH), 129.2 (CH), 129.6 (2 × CH), 129.9 (CH), 133.7 (2 × C), 135.6 (4 × CH), 137.9 (C), 150.7 (CH) ppm. MS (CI) *m*/*z* (%) 499 (6), 497 (4), 485 (32), 119 (100). HRMS (CI) calcd for $C_{25}H_{36}OSiSn$, 499.1478; found, 499.1479.

11-*cis*-*tert*-Butyldiphenylsilyl retinyl ether (15). Suzuki reaction with iodide: To a suspension of $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) and pinacol dienylboronate **4b** (447 mg, 0.96 mmol) in THF (4 mL) was added, via cannula, a solution of trienyl iodide **2b** (153 mg, 0.48 mmol) in THF (5 mL). A solution of TlOH (10% in water, 2.1 mL, 0.96 mmol) was added dropwise, and stirring was continued for 5 h. The mixture was filtered through a short pad of neutral alumina and concentrated, and the crude was purified by flash chromatography (Al_2O_3, hexane), yielding 183 mg (73%) of **15** as an unstable pale yellow oil. **Suzuki reaction with triflate:** To a suspension of $Pd(PPh_3)_4$ (34 mg, 0.029 mmol), K_3PO_4 (123 mg, 0.58 mmol) and pinacol dienylboronate **4b** (300 mg, 0.65 mmol) in THF (7 mL) was added, via cannula, a solution of trienyl triflate **3** (100 mg, 0.29 mmol) in THF (3 mL), and the reaction mixture was stirred for 5 h, filtered through a short pad of neutral alumina (IV, hexane), and concentrated. The crude was purified by flash chromatography (Al_2O_3, hexane), yielding 114 mg (76%) of **15**. **Stille reaction with iodide:** To a solution of trienyl iodide **2b** (35 mg, 0.11 mmol) and trimethyldienylstannane **6** (108 mg, 0.22 mmol) in DMF (4 mL) were added, sequentially, CsF (34 mg, 0.22 mmol), $Pd(PPh_3)_4$ (6 mg, 0.006 mmol) and CuI (3 mg, 0.011 mmol). The reaction mixture was stirred for 3 h at room temperature, filtered through a short pad of neutral alumina, and concentrated. Flash chromatography of the crude (Al_2O_3, hexane) afforded 50 mg (86% yield) of **15**. **Stille reaction with triflate:** To a solution of trienyl triflate **3** (47 mg, 0.13 mmol) and trimethyldienylstannane **6** (76 mg, 0.15 mmol) in NMP (4 mL) were added, each in one portion, $Pd_2(dba)_3{\cdot}CHCl_3$ (4.0 mg, 0.003 mmol) and $AsPh_3$ (8.0 g, 0.03 mmol), and the reaction mixture was stirred for 6 h, filtered through a short pad of neutral alumina, and concentrated. Flash chromatography of the crude (Al_2O_3, hexane) yielded 58 mg (81%) of **15**. ^{1}H NMR (750 MHz, $CDCl_3$) δ 1.03 (s, 6H), 1.05 (s, 9H), 1.4−1.5 (m, 4H), 1.5−1.6 (m, 4H), 1.67 (s, 3H), 1.70 (s, 3H), 1.94 (s, 3H), 2.01 (t, J = 6.1 Hz, 2H), 4.34 (d, J = 6.2 Hz, 2H), 5.76 (t, J = 6.2 Hz, 1H), 5.86 (d, J = 11.8 Hz, 1H), 6.11 (d, J = 16.1 Hz, 1H), 6.17 (d, J = 16.1 Hz, 1H), 6.33 (t, J = 11.8 Hz, 1H), 6.55 (d, J = 11.8 Hz, 1H), 7.3−7.4 (m, 6H), 7.6−7.7 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (CH_3), 17.2 (CH_3), 18.8 (C), 19.3 (CH_2), 21.7 (CH_3), 26.8 (3 × CH_3), 28.9 (2 × CH_3), 33.0 (CH_2), 34.3 (C), 39.6 (CH_2), 61.4 (CH_2), 124.7 (CH), 126.5 (CH), 126.7 (CH), 127.6 (4 × CH), 129.1 (C), 129.5 (2 × CH), 131.1 (CH), 132.9 (CH), 133.8 (2 × C), 135.5 (4 × CH), 136.8 (C), 137.7 (C), 137.9 (C), 138.2 (CH) ppm. MS (CI) *m*/*z* (%) 524 (59), 523 (13), 273 (44), 269 (61), 199 (100). HRMS (CI) calcd for $C_{36}H_{48}OSi$, 524.3474; found, 524.3476.

11-*cis*-Retinol (16). TBAF (1.0 M in THF, 0.3 mL, 0.30 mmol) was added to a solution of retinyl ether **15** (80 mg, 0.15 mmol) in THF (5 mL), and the resulting solution was stirred for 90 min. The solvent was removed under vacuum, and the crude was purified by flash chromatography (SiO_2, 70:29:1 hexane/AcOEt/Et_3N), affording **16** as a yellow oil (41 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 6H), 1.4−1.5 (m, 2H), 1.5−1.6 (m, 2H), 1.71 (s, 3H), 1.89 (s, 3H), 1.93 (s, 3H), 2.01 (t, J = 6.3 Hz, 2H), 4.29 (t, J = 6.8 Hz, 2H), 5.72 (t, J = 6.8 Hz, 1H), 5.87 (d, J = 11.8 Hz, 1H), 6.08 (d, J = 16.1 Hz, 1H), 6.17 (d, J = 16.1 Hz, 1H), 6.35 (t, J = 11.8 Hz, 1H), 6.56 (d, J = 11.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2 (CH_3), 17.2 (CH_3), 19.3 (CH_2), 21.8 (CH_3), 28.9 (2 × CH_3), 33.0 (CH_2), 34.2 (C), 39.6 (CH_2), 59.5 (CH_2), 125.3 (CH), 126.2 (CH), 127.1 (CH), 129.2 (C), 130.1 (CH), 132.4 (CH), 136.5 (C), 137.3 (C), 137.9 (C), 138.0 (CH) ppm. IR ($CHCl_3$) ν 3417 (f, O−H), 2925 (f, CH) cm^{-1}. MS (CI) *m*/*z* (%) 286 (55), 269 (100), 199 (34), 179 (29), 90 (70). HRMS (CI) calcd for $C_{20}H_{30}O$, 286.2297; found, 286.2290

11-*cis*-Retinal (1). To a suspension of $BaMnO_4$ (28 mg, 0.11 mmol)) in CH_2Cl_2 (2 mL) was added, dropwise, a solution of 11-*cis*-retinol (**16**; 10 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL), and the resulting mixture was stirred for 6 h, filtered through a short pad of neutral alumina (IV, hexane), and concentrated. Flash chromatography of the crude (Al_2O_3, hexane) afforded 11-*cis*-retinal (**1**) as an unstable yellow oil (9 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 6H), 1.4−1.5 (m, 2H), 1.5−1.6 (m, 2H), 1.71 (s, 3H), 1.99 (s, 3H), 2.02 (t, J = 5.8 Hz, 2H), 2.35 (s, 3H), 5.91 (d, J = 11.8 Hz, 1H), 6.08 (d, J = 8.0 Hz, 1H), 6.13 (d, J = 16.0 Hz, 1H), 6.34 (d, J = 16.0 Hz, 1H), 6.53 (d, J = 12.4 Hz, 1H), 6.68 (dd, J = 12.4, 11.8 Hz, 1H), 10.01 (d, J = 8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4 (CH_3), 18.0 (CH_3), 19.2 (CH_2),

21.8 (CH_3), 29.0 (2 × CH_3), 33.0 (CH_2), 34.3 (C), 39.5 (CH_2), 125.7 (CH), 129.7 (2 × CH), 130.1 (CH), 130.2 (C), 131.5 (CH), 137.4 (CH), 137.6 (C), 141.7 (C), 155.9 (C), 191.2 (CH) ppm. IR ($CHCl_3$) υ 1727 (f), 1661 (f, CHO) cm^{-1}. MS (CI) *m*/*z* (%) 285 ($M^+ + 1$, 68), 284 (20), 149 (26), 29 (100). HRMS (CI) calcd for $C_{20}H_{29}O$, 285.2218; found, 285.2219.

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Supporting Information Available: General methods, experimental procedures for compounds **12**−**14**, tables of spectroscopic data, and ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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