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A Comprehensive Survey of Stille-Type C_{sp^2}–C_{sp^2} Single Bond Forming Processes in the Synthesis of Retinoic Acid and Analogs

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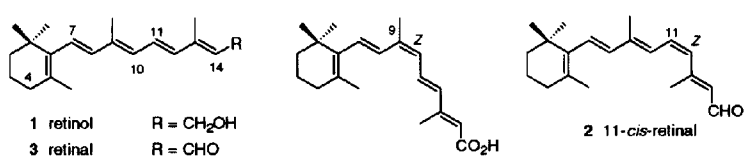
Abstract. The synthesis of the retinoid skeleton has been exhaustively explored using the Stille coupling for the formation of the side-chain single bonds. On employing the experimental catalytic conditions developed by Farina [$Pd_2(dba)_3$, $AsPh_3$, NMP] we have modified the electronic and steric requirement of the coupling partners, alkenyl stannanes and electrophiles (alkenyl iodides and triflates). The comprehensive survey afforded appropriately matched components for every bond formation considered. Moreover, from the comparison of the reactivities of different coupling partners with different degrees of steric hindrance, the sensitivity of the Stille coupling to steric effects was confirmed. Besides providing a variety of building blocks for retinoid synthesis, the study highlights some trends that might be useful for the application of the Stille reaction to the synthesis of unsubstituted conjugated polyenes.

Keywords: Retinoids; Stille reaction; Polyenes; Stereocontrol.

Introduction

The term retinoids[1] collectively refers to a group of natural and synthetic analogs of retinol (vitamin A, **1**) that have important biological roles during the development of the embryo and in postnatal life. These biological activities are structurally dependent upon the nature of the end group and the geometry of the polyene side chain. Vitamin A (**1**) is responsible for the normal development of many cell types.[2] Retinaldehydes act as chromophores of photoreceptor proteins. 11-*cis*-Retinal (**2**) is present in the light-capturing device that triggers the neural signal in the visual system,[3] and *trans*-retinal (**3**) is a component of the light-harvesting device coupled to the ion-pumps of Halobacteria.[4] More recently, *trans*-retinoic acid (**4**) and 9-*cis*-retinoic acid (**5**) have been identified as the natural ligands of the retinoid subfamily of nuclear receptors (retinoic acid receptors, RAR's, subtypes α, β and γ; and retinoid X receptors, RXR's, subtypes α, β and γ) and these compounds function as transcription factors.[5] These proteins, upon ligand activation, are capable of influencing cell proliferation and cell differentiation processes under the control of the responsive genes, thus transducing the pleiotropic effects of retinoids on morphogenesis, differentiation and homeostasis.

Figure 1



1 retinol R = CH_2OH
3 retinal R = CHO
4 retinoic acid R = CO_2H

2 11-*cis*-retinal

5 9-*cis*-retinoic acid

A general classification of synthetic routes to the retinoid polyene skeleton[6] distinguishes two processes, double and single bond forming reactions, and labels the building blocks according to the number of carbon atoms they contribute to the final diterpene skeleton.[6] Wittig (and Horner–Wadsworth–Emmons, HWE) condensations,[7]

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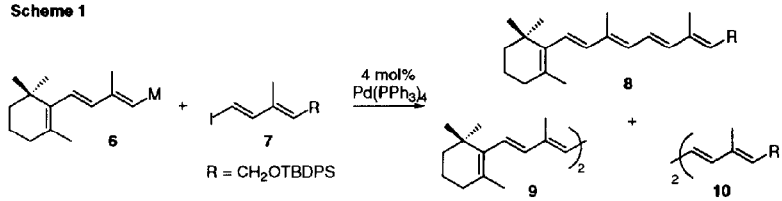
and Julia olefinations[8] are among the most often used double-bond forming reactions. The synthesis of polyenes involving C–C single-bond formation usually features metal-catalyzed (notably palladium and nickel) cross-coupling reactions between alkenyl organometallic reagents and alkenyl electrophiles.[9,10] Boronic acids,[11] organoaluminum compounds,[12] organozinc derivatives[13] and organostannanes[14] as alkenyl organometallic partners have been used with variable success.

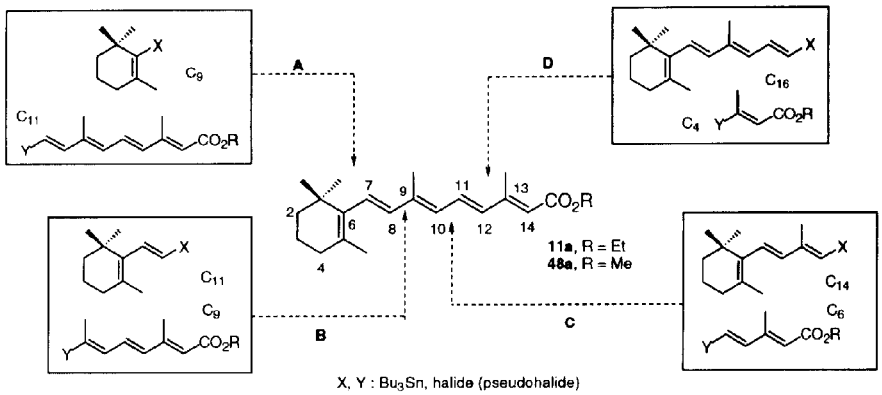
Negishi and Owczarczyk[15] recently carried out a comprehensive study of the efficacy of different metals in the palladium-catalyzed [$Pd(PPh_3)_4$] cross-coupling of trienylmetal derivative **6** and dienyl iodide **7** (Scheme 1) in the synthesis of vitamin A (**1**). Whereas alkenyl organozinc reagents (**6**, M = $Zn_{1/2}$) provided the pentaene **8** in good yield (87%), other metals [**6**, M = $AlMe_2$, $Mg_{1/2}$, $SnMe_3$, CuMgX, $B(OR)_2$, and $ZrCp_2Cl$] proved less efficient, particularly the last four, with concomitant formation of dimers of both coupling partners (**9** and **10**).

Scheme 1



Clarification of reaction mechanisms and fine-tuning of reaction conditions (metals, ligands, solvent, additives) have led to significant rate enhancements in metal-catalyzed cross-coupling reactions. We have adopted Kishi's variant of the Suzuki coupling (*i.e.* the use of thallium hydroxide) to enhance the coupling rate of boronic acids and electrophiles in a new, mild, route to vitamin A (**1**) and its side-chain desmethylated analogs.[11e] We felt that the Stille coupling using organostannanes might also be optimized for retinoid synthesis, particularly since at the inception of this work comprehensive studies into the effects of ligands and additives had been published.[16,17] Mainly through the work of Farina, Liebeskind and coworkers, it was established that the use of ligands of lower donicity towards Pd(II) [e.g. triphenylarsine and tri(2-furyl)phosphine][16] and the addition of copper(I) salts,[17] could lead to dramatic rate enhancement (up to 10^3) in the Stille reaction. We have recently described that this rate accelerating effect can be used for the preparation of retinoic acid (**4**) and its ring-modified derivatives by coupling of hindered cycloalkenyl triflates and tetraenyl stannanes.[18] We wish to report here a complete account of our work, which includes the exploration of all the polyene side-chain single-bond forming reactions required to construct the model system ethyl (or methyl) retinoate (**11a**).[19] In order to assess which of the strategies would prove most promising, we performed key-step coupling reactions to construct bonds C6–C7 (A, Scheme 2), C8–C9 (B), C10–C11 (C), and C12–C13 (D), in a convergent fashion. This approach required the preparation of the complementary coupling partners, functionalized as either alkenyl stannanes or as electrophiles (alkenyl halide, alkenyl triflate), ranging in complexity from vinyl to tetraenyl building blocks (Scheme 2). The availability of the starting materials required to obtain the coupling partner, the yields of the transformations involved, and the efficiency of the coupling step would dictate the merit of each disconnection and, accordingly, its potential application to retinoid synthesis. As a representative of the natural polyenes, the routes to retinoids described in this article might provide alternatives to more traditional approaches to fully conjugated compounds.[20]

Scheme 2



Results and Discussion

C6–C7 DISCONNECTION (A, SCHEME 2)

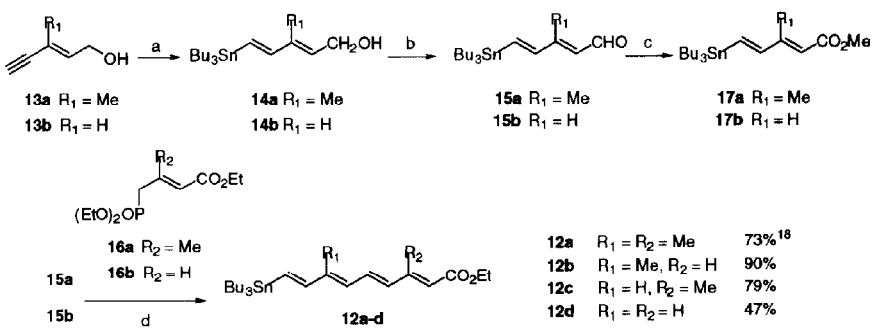
a) C_9-Cyclohexenyl triflate and C_{11}-tetraenyl stannane

In our previous study describing the main features of this disconnection,[18] we examined a variety of reaction conditions and concluded that the modification of the Stille coupling reported by Farina [$Pd_2(dba)_3$ (2.5 mol%) and $AsPh_3$ (20 mol%) as a catalyst in NMP] afforded the highest yield without compromising the stereochemical integrity of the side chain. Under these conditions, which were adopted as the general procedure, the coupling of cyclohexenyl triflates and tetraenyl stannanes (see Scheme 4 and Table 1) provided good yields of ethyl retinoate (**11a**, R = Et) and its analogs. The dimerization of tetraenyl stannane **12a** was the main competing reaction, and the yield of the dimer was shown to be largely related to the steric hindrance of the starting triflates. Such dimerization was insignificant as the temperatures required for the coupling became milder (*i.e.* for the less-substituted cycloalkenyl triflates). Despite this shortcoming, the approach is very versatile since the commercially available starting ketones can be regioselectively converted into the corresponding kinetic or thermodynamic triflates[21] and hence into the pentaenes. Moreover, the structure of the tetraenyl stannane **12** can be easily modified by a suitable choice of starting materials, with the advantage of an additional gain in diversity. Accordingly, we extended the study to the preparation of side-chain desmethylated retinoids **11b–d** (Table 1).

Functionalized tetraenyl stannanes **12b–d** were synthesized by the same routes as used for the preparation of **12a**, which involved the HWE condensation of the carbanion of either ethyl (*E*)-4-(diethoxyphosphinoyl)-3-methyl-but-2-enoate **16a**[22] or ethyl (*E*)-4-(diethoxyphosphinoyl)but-2-enoate **16b** with stannyldienals[23] **15a**[23a] and **15b**.[23b] The reaction provided access to tetraenyl stannanes **12a–d** in good chemical yield and with good stereochemical purity. With *n*-BuLi as a base, the best yields were obtained when DMPU was added to THF for the generation of the carbanion (0 °C).[24] For the more labile unsubstituted polyenes, recourse was made to the

use of LiHMDS in the presence of HMPA before the addition of aldehydes **15**. The incorporation of the tri-*n*-butylstannyl group into dienes **15** relied on the stannylcupration of the commercial precursor enynols **13a** and **13b**, according to the procedure pioneered by Lipshutz *et al.*[25] and optimized in regio- and stereoselectivity by Pancrazi *et al.*[26] Addition of the mixed cuprate reagent (*n*-Bu_3Sn)(Bu)CuLi·LiCN[27] to a solution of enynols **13a** or **13b**, followed by quenching with MeOH, provided stannyldienols **14a**[23a] and **14b**[23b] (Scheme 3). Oxidation of **14a** and **14b** to aldehydes **15a** (96%) and **15b** (70%), respectively, was best accomplished[23a] with the Doering-Parikh reagent, by treatment with SO_3·Py (3 equiv) and Et_3N (3 equiv) in CH_2Cl_2/DMSO (1:1) at 0 °C.[28] Scheme 3 also depicts the transformation of aldehydes **15a** and **15b** to esters **17a** (82%) and **17b** (98%), respectively, which were subsequently used in later stages of this work, by treatment of **15a** and **15b** with MnO_2 and KCN in MeOH at 0 °C.[29]

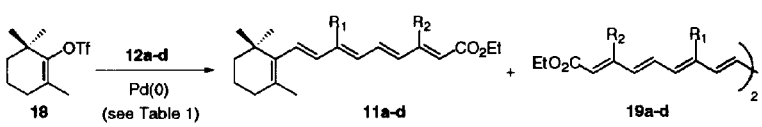
Scheme 3[a]



[a] (a) (*n*-Bu_3Sn)(Bu)CuLi·LiCN (ref. 23). (b) SO_3·Py (3 equiv), Et_3N (3 equiv), CH_2Cl_2/DMSO (1:1), 0 °C, 96% for **15a**, 70% for **15b**. (c) MnO_2, KCN, MeOH, 0 °C, 82% for **17a**, 98% for **17b**. (d) *i.* *n*-BuLi, DMPU, THF, 0 °C for **12a** and **12c** or LiHMDS, HMPA, - 78°C for **12b** and **12d**; *ii.* aldehyde **15**, -78 -> -20 °C.

Application of the modified Stille reaction conditions reported by Farina, as described for the coupling of **12a** and **18**,[18] to the series of desmethylated tetraenyl stannanes provided pentaenes **11a–d** together with variable amounts of the octaenes **19a–d** (Scheme 4 and Table 1).

Scheme 4



It is interesting to note that whereas the methyl group at C3 in **12** does not significantly affect the reactivity of the stannane (entries 1 and 2), its presence at C7 (closer to the tri-*n*-butylstannyl substituent) severely retards the coupling rate (*cf.* entries 1 and 2 *vs* 3 and 4). As a consequence of the lower temperature required for the coupling of **18** to **12c** or **12d**, the yields are improved (entries 3 and 4) relative to those of **12a** and **12b**. Since

the absorption properties of the tetraenyl stannanes [**12a**, λ_{max} 334 nm (ε 20 100); **12b**, λ_{max} 344 nm (ε 24 100); **12c**, λ_{max} 336 nm (ε 18 900); **12d**, λ_{max} 336 nm (ε 15 900)] are not significantly divergent, the rate difference is not likely to be due to deviations from planarity arising from steric interactions of the methyl substituents and their neighbouring groups. Perhaps subtle steric interference between the C7-methyl substituent and other groups present in some of the intermediates of the catalytic cycle[30] must be invoked in order to explain the significant rate differences that were qualitatively observed.

Table 1.[a] *Stille coupling between cyclohexenyl triflate **18** and tetraenyl stannanes **12a–d***

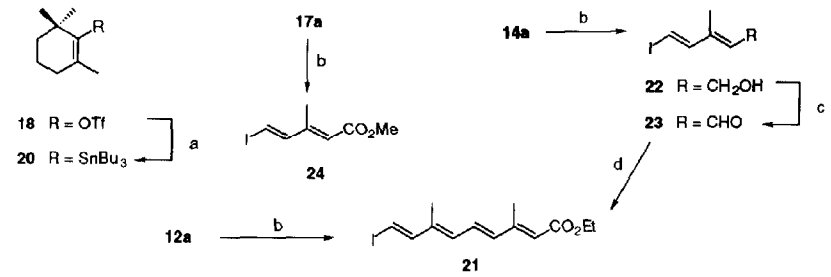
Entry	R_1	R_2	T (°C)	t (h)	Yield (%)[b]	Dimer Yield (%)[c]
1[18]	Me	Me	70	2	**11a** (62)	**19a** (30)
2	Me	H	70	2	**11b** (75)	**19b** (30)
3	H	Me	50	2	**11c** (87)	**19c** (22)
4	H	H	50	2	**11d** (85)	**19d** (22)[d]

[a] Reaction conditions: 2.5 mol% $Pd_2(dba)_3$, 20 mol% $AsPh_3$ and 1:1.1 triflate/stannane molar ratio in NMP. [b] Yield based on starting triflate. [c] Yield based on starting stannane. Reaction temperature (10 °C increments) indicated is the one at which evidence for conversion to the product was seen by tlc after 15 min stirring. [d] Highly unstable; it could not be fully characterized.

b) C_9-Cyclohexenyl stannane and C_{11}-tetraenyl iodide

The reversal of functionality in approach A required the preparation of cyclohexenyl stannane **20** and tetraenyl iodide **21**, both of which could be obtained starting from the previously prepared fragments **18** and **12a**, respectively. Alkenyl triflate **18** was converted to alkenyl stannane **20** in 68% yield by reaction with the corresponding "higher order" cyanocuprate according to the conditions described by Wulff.[31] On the other hand, although treatment of tetraenyl stannane **12a** with a solution of iodine in CH_2Cl_2[32] provided the iodide **21**, this was shown to be a complex mixture of *E/Z* isomers. The erosion of the geometric integrity in the direct preparation of **21** is most likely due to an iodine-induced isomerization process acting either on **12a** or on **21**. Stereochemically homogeneous *E*-**21** was alternatively obtained by HWE condensation of iodide **23** (Scheme 5) and phosphonate **16a** under the conditions specified in Scheme 5. Compound **21** proved to be highly unstable and it was therefore used immediately after preparation. Treatment of stannane **20** with either tetraenyl iodide **21** or even the shorter dienyl iodide **24** (derived from **17a** by tin-iodine exchange, see Scheme 5) under Pd-catalyzed conditions led to recovery of starting materials in both cases. The reluctance of stannane **20** to react with iodides is likely to be a result of severe steric hindrance about the carbon-tin bond.

Scheme 5[a]



[a] (a) (*n*-Bu_3Sn)(Bu)CuLi·LiCN, THF, - 30 °C, 68%. (b) I_2, CH_2Cl_2, -20 °C, 72% for **22**, 90% for **24**. (c) MnO_2, CH_2Cl_2, 89%. (d) *i.* *n*-BuLi, DMPU, **16a**, THF, 0 °C, - 78 °C; *ii.* aldehyde **23**, -78 °C, 87%.

C8-C9 DISCONNECTION (B, SCHEME 2)

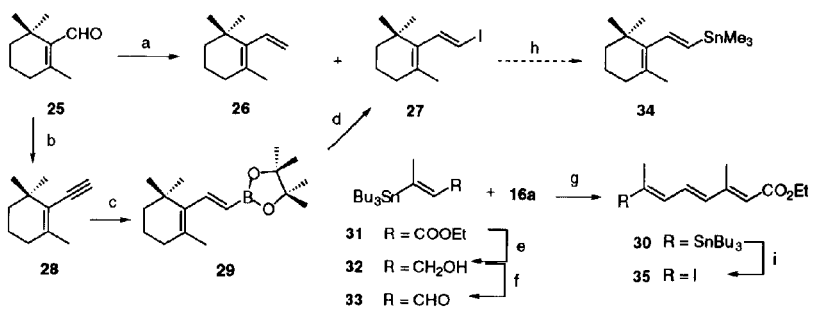
The approach to ethyl retinoate (**11a**) using this bond formation requires dienyl and trienyl partners functionalized as stannanes or electrophiles.

a) C_{11}-Dienyl electrophile and C_9-trienyl stannane

The starting material of choice for the preparation of the C_{11}-dienyl fragment is β-cyclocitral (**25**), which was expected to afford iodide **27** in a straightforward manner.[33] However, due to its sterically hindered carbonyl group, sluggish conversion to a mixture of products, and mostly recovery of starting material, was observed upon treatment of **25** with a reactive chromium species generated *in situ* from CHI_3 and $CrCl_2$ at 25 °C for 20 h according to Takai's procedure.[33] Alternatively, alkenyl iodides can be prepared by Wittig condensation between a carbonyl compound and the ylide derived from $Ph_3PCH_2I_2$.[34] Stereoselectivity is a function of the base and the reaction temperatures employed for the condensation. While Stork's conditions [NaHMDS, HMPA, THF] at –78 °C favor the *Z*-alkenyl iodide, higher temperatures result in erosion of *Z*-selectivity in favor of the *E*-isomer. For the sterically hindered β-cyclocitral (**25**), it was considered likely that the reaction was already biased towards the desired *E*-alkenyl iodide **27** even at moderate temperatures. In accordance with our expectations, generation of the ylide with NaHMDS, in a THF-HMPA mixture at –60 °C, followed by addition of aldehyde **25** and further stirring at –23 °C, provided stereochemically pure *E*-alkenyl iodide **27**, albeit in low yield (34%). However, in addition to **27** variable amounts of the known diene **26**[35] (~50%) (Scheme 6) were also formed, and this compound might arise by halogen-metal exchange under the reaction conditions. Alternatively, iodide **27** could be obtained through selective functionalization of known alkyne **28**.[1] Enyne **28** was obtained in good yield (74%) upon treatment of **25** with TMSC(Li)N_2 [generated *in situ* by addition of LDA to (trimethylsilyl)diazomethane at –78 °C][36] in THF at –78 °C.[37] Hydroboration of alkyne **28** using pinacol borane[38] regio- and stereoselectively provided boronic ester **29** (46% based on recovered starting alkyne **28**). Boron-halogen exchange with MeONa at –78 °C followed by addition of ICl[39] stereoselectively provided alkenyl iodide **27** in 65% yield (Scheme 6), thus completing the preparation of one of the required alkenyl fragments.

Tricnyl stannanes have not been widely described in the literature, and those that have are mainly in the context of total synthesis of polyene natural products.[40] The preparation of the triene system invariably uses the Wittig or HWE condensations. Since tetraenyl stannanes **12** were efficiently synthesized using this methodology, it seemed reasonable to prepare **30** through condensation of aldehyde **33** and the anion derived from the treatment of **16a** with base. Aldehyde **33** could, in turn, be obtained by adjustment of the oxidation state starting from known ethyl (*E*)-3-(tri-*n*-butylstannyl)but-2-enoate (**31**), the product of stannylcupration of ethyl tetrolate.[41] Reduction to **32** (LAH, ether, 0 °C)[42] was followed by oxidation with MnO_2 (18 equiv) in CH_2Cl_2 in the presence of Na_2CO_3 (18 equiv), which provided **33** as a single geometric isomer in 85% yield (Scheme 6). For the condensation step, aldehyde **33** was added, at –78 °C, to the carbanion derived from **16a** (generated by slow addition of *n*-BuLi in THF-DMPU at 0 °C), and further stirring at –20 °C for 2 h finally gave **30** in 74% yield (Scheme 6).

Scheme 6[a]



[a] (a) *i*. $Ph_3PCH_2I^+I^-$, NaHMDS, HMPA, THF, -60 °C; *ii*. aldehyde **25**, THF, -23 -> 25 °C, **27**, 34%; **26**, 50%. (b) *i*. LDA, $(TMS)CHN_2$, THF, -78 °C; *ii*. aldehyde **25**, THF, -78 -> 25 °C, 74%. (c) *i*. pinacol, $BH_3{\cdot}SMe_2$, CH_2Cl_2, 0 -> 25 °C; *ii*. enyne **28**, CH_2Cl_2, 0 -> 50 °C, 46%. (d) *i*. MeONa, MeOH, THF, -78 °C; *ii*. ICl, CH_2Cl_2, -78 °C, 65%. (e) $LiAlH_4$, ether, 0 °C, 72%. (f) MnO_2, Na_2CO_3, CH_2Cl_2, 25 °C, 85%. (g) *i*. *n*-BuLi, DMPU, **16a**, THF, 0 °C; *ii*. aldehyde **33**, -78 -> -20 °C, 74%. (h) *i*. *t*-BuLi, THF, -78 °C; *ii*. Me_3SnCl, THF, -78 °C. (i) I_2, CH_2Cl_2, 0 °C, 98%.

Coupling of fragments **27** and **30** under the optimized Stille conditions led to ethyl retinoate (**11a**) in 56% yield after stirring in the presence of the palladium catalyst and ligands at 50 °C for 3 h.

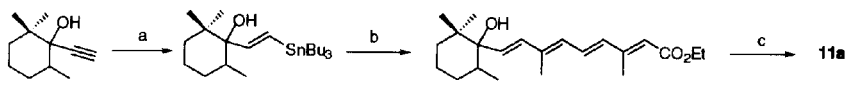
b) C_{11}-Dienyl stannane and C_9-trienyl iodide

This variation could not be investigated due to the inefficient synthesis of dienyl stannane **34** from its potential precursors (Scheme 6). Whereas trienyl stannane **30** was smoothly converted to trienyl iodide **35** in high yield (98%) upon treatment with a solution of iodine in CH_2Cl_2 at 0 °C,[32] low yields and/or mixtures of *E*/*Z* isomers were obtained in attempts to trap with Me_3SnCl the anion generated by treatment of dienyl iodide **27** with *t*-BuLi at – 78 °C. The same result was obtained in the stannylcupration of enyne **28**.[35,26] Likewise, attempts to directly convert aldehyde **25** with the chromium-tin reagent described by Hodgson,[43] even under optimized conditions, led to recovery of **25**.

c) C_{11}-Alkenyl stannane and C_9-trienyl iodide

Given the shortcomings of the above approach, yet another alternative was sought. Vinyl stannane **37** could be stereoselectively obtained based on precedents involving the palladium-catalyzed tributyl stannane addition[26a] to a propargyl alcohol structurally similar to **36**,[35] and it seemed reasonable to include this in the study in order to evaluate its utility in retinoid synthesis. In the event, addition of tributyl stannane to known alkynol **36**[35] in the presence of catalytic quantities of $PdCl_2(PPh_3)_3$ provided alkenyl stannane **37** in 60% yield. Coupling of **37** and trienyl iodide **35** (Scheme 6) required prolonged reaction times (60 °C, 16 h) and provided stereochemically homogeneous tetraene **38** in 54% yield (Scheme 7). Dehydration to ethyl retinoate **11a** proceeded smoothly in high yield (85%) upon stirring a solution of **38** in benzene with a catalytic amount of *p*-TsOH at room temperature for 1.5 h.[44]

Scheme 7[a]



36 **37** **38**

[a] (a) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnH, THF, 25 °C, 60%. (b) **35**, $Pd_2(dba)_3$, $AsPh_3$, NMP, 60 °C, 16 h, 54%. (c) *p*-TsOH, benzene, 25 °C, 1.5 h, 85%.

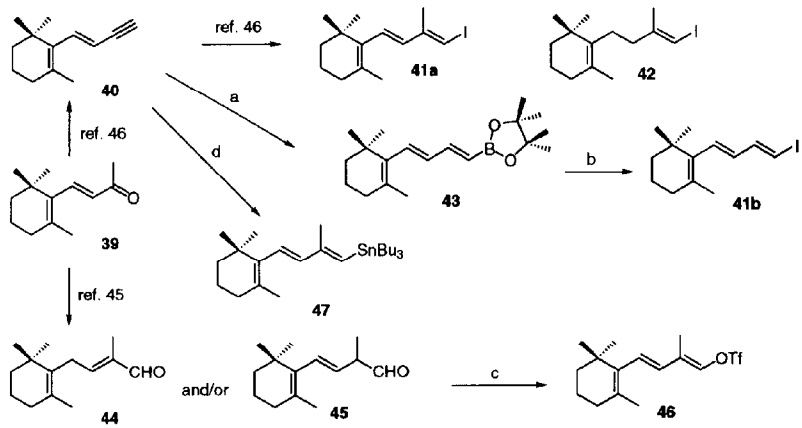
C10-C11 DISCONNECTION (C, SCHEME 2)

a) C_6-Dienyl stannane and C_{14}-trienyl iodide

As in approach **B**, the C10–C11 bond-forming process requires the coupling of appropriately functionalized dienyl and trienyl fragments. This is the most straightforward convergent approach in terms of relative ease of preparation of the required units, since the preparation of iodide **41a** by zirconocene-mediated carboalumination followed by iodination of alkyne **40**, derived from β-ionone (**39**), has already been described (Scheme 8).[45] Vinyl iodide **42** has also been described, starting from the same commercial ketone **39**.[45] Availability of both iodides **41a** and **42** allows the estimation of the relative rate of coupling of dienyl stannanes **17a,b** (Scheme 3) to either trienyl or alkenyl iodides. On the other hand, the desmethylated analog **41b** provides additional structural variation, leading to the preparation of side-chain-modified analogs. The synthesis of **41b** was achieved by the stereoselective boron-halogen exchange described above,[39] starting from pinacol boronic ester **43** (87% yield).

Additionally, since isomeric C_{14}-aldehydes **44** or **45** can be easily prepared from β-ionone (**39**) by Darzens condensation,[46] trienyl triflate **46** was also selected as an alternative coupling partner to iodide **41a**. Alkenyl triflates are usually obtained from aldehydes through reaction with triflic anhydride in the presence of a non-nucleophilic base (such as 2,6-di-*tert*-butyl-4-methylpyridine, DBMP)[47] and subsequent decomposition of the *gem*-bistriflate intermediates.[48] In the event, treatment of aldehyde **44** with the triflating agent and base in CH_2Cl_2 at 0 °C, followed by heating to 50 °C for 1 h,[49] provided trienyl triflate **46**, albeit in low yields (30–40%), whereas complex mixtures were obtained upon treatment of the non-conjugated isomer **45** under the same conditions (Scheme 8).

Scheme 8[a]

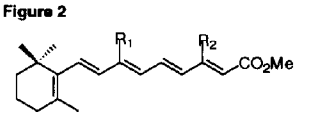


[a] (a) *i.* pinacol, $BH_3{\cdot}SMe_2$, CH_2Cl_2, 0 -> 25 °C; *ii.* enyne **40**, CH_2Cl_2, 0 -> 50 °C, 55%. (b) *i.* MeONa, MeOH, THF, -78 °C; *ii.* ICl, CH_2Cl_2, -78 °C, 87%. (c) Tf_2O, DBMP, CH_2Cl_2, 0 -> 25 °C, 30-40%. (d) ref. 51.

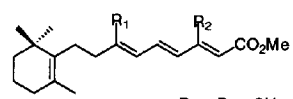
The fragments prepared in this way were subjected to the standard coupling conditions described above within the temperature range 50 to 80 °C. Depending upon structural variations, the reactions afforded retinoids **48a–d** in good to excellent yields and the results are listed in Table 2.[50] As in the coupling of tetraenyl stannanes (approach A), the methyl substituent in the vicinity of the tin-vinyl carbon bond had a retarding effect on the coupling rate (*cf.* entries 2 and 4 *vs.* 1 and 3). The greater reactivity of **17b** relative to **17a** can be attributed to the presence of the substituent vicinal to the electrophile on the latter (entries 1 and 3). The coupling of **17b** to the non-conjugated vinyl iodide **42** was slowed down even further relative to the trienyl iodide **41a**, and this result might be interpreted as being due to the greater steric congestion in the transition state involving the conformationally more flexible electrophile **42**.

On the other hand, trienyl triflate **46** coupled in almost quantitative yield (98%) with dienyl stannane **17a** to give methyl retinoate (**48a**) after 30 minutes at 60 °C (entry 7).

Figure 2



48 a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$, $R_2 = H$
c, $R_1 = H$, $R_2 = CH_3$
d, $R_1 = R_2 = H$



49 a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$, $R_2 = H$

Table 2.[a] *Stille coupling between C_{14}-alkenyl electrophiles and C_6-dienyl stannanes*

Entry	Electrophile	Stannane	T (°C)[b]	t(h)	Retinoid	Yield (%)
1	**41a**	**17a**	60	3	**48a**	64
2	**41a**	**17b**	50	0.5	**48b**[50]	73
3	**41b**	**17a**	50	5	**48c**[50]	67
4	**41b**	**17b**	50	0.5	**48d**[50]	81
5	**42**	**17a**	80	3	**49a**	87
6	**42**	**17b**	80	1	**49b**	80
7	**46**	**17a**	60	0.5	**48a**	98

[a] Reactions carried out with 2.5 mol% $Pd_2(dba)_3$, 20 mol% $AsPh_3$, and a 1:1.1 iodide or triflate/stannane molar ratio in NMP. [b] Reaction temperature indicated (10 °C increments) is the one at which evidence for conversion to the product was seen by tlc after 15 min stirring.

b) C_6-Trienyl stannane and C_{14}-dienyl iodide

This is the same modification as previously reported by Negishi in the synthesis of vitamin A.[15] The exchange of functionality is straightforward since trienyl stannane **47** can be directly obtained[51] from enyne **40** by stannylcupration-methylation, and dienyl stannane **17a** can be easily converted (90%) to dienyl iodide **24** (Scheme 5). Coupling of components **47** and **24** under the specified conditions took place at 50 °C in 3 h to provide methyl retinoate (**48a**) in an unoptimized yield of 76%. The efficiency of this approach is reinforced by a recent report in which use of the free carboxylic acid derived from **24** is described. In that case retinoic acid (**4**) was obtained in 73% yield [$PdCl_2(CH_3CN)_2$, DMF, 25 °C, 3h].[51]

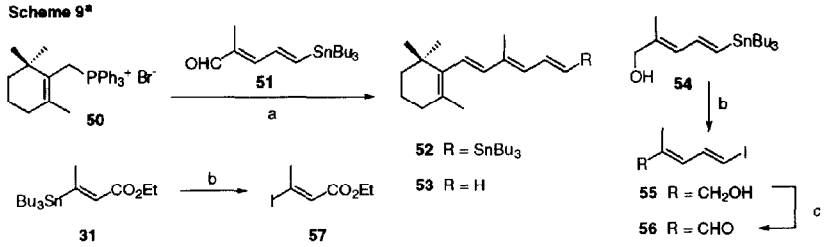
C12-C13 DISCONNECTION (D, SCHEME 2)

The terminal alkenyl-alkenyl disconnection (C12–C13 bond) involves, as in disconnection A, the preparation of fragments with tetraenyl and enyl structures. Compared to alternative A, the coupling was expected to take place under considerably milder conditions, since the required partners have less demanding steric congestion.

a) C_{16}-Tetraenyl stannane and C_4-alkenyl iodide

The preparation of the C_{16}-tetraenyl stannane featured a Wittig condensation of phosphonium salt **50**[52] and known stannyl aldehyde **51**.[53] Treatment of **50** with *n*-BuLi in THF at 0 °C for 30 min, addition of aldehyde **51** at 0 °C, and further stirring at 25 °C for 6 h, provided tetraenyl stannane **52** in 77% yield after purification by reversed-phase column chromatography.[54] Without this precaution, hydrocarbon **53** results upon protodestannylation of **52** (Scheme 9). On the other hand, vinyl stannane **31** was treated with I_2 in CH_2Cl_2,[32] to provide vinyl iodide **57**. In accordance to our expectations, coupling of fragments **52** and **57** under the standard catalytic conditions took place at room temperature to afford ethyl retinoate **11a** in 97% yield.

Scheme 9[a]



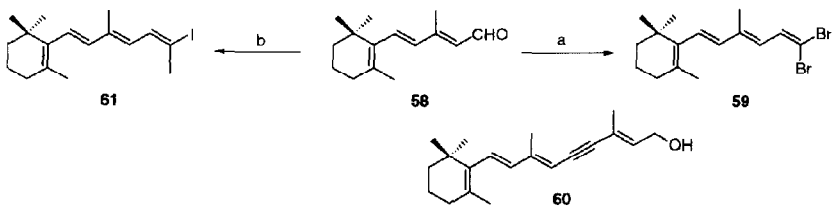
[a] (a) *i.* *n*-BuLi, THF, 0 °C; *ii.* aldehyde **51**, THF, 0 -> 25 °C, 77%; (b) I_2, CH_2Cl_2, 25 °C, 79% for **55**, 67% for **57**; (c) MnO_2, CH_2Cl_2, 25 °C, 90%.

b) C_{16}-Tetraenyl iodide and C_4-alkenyl stannane

Alternatively, iodide **56**,[55] obtained by tin-iodine exchange of dienyl stannane **54** followed by oxidation of the allylic alcohol **55**, was considered a convenient precursor of a C_{16} tetraenyl iodide that, by coupling to stannane **31**, would afford the desired retinoid **11a** (Scheme 9). However, coupling of iodide **56** to phosphonium salt **50** proved less efficient than coupling of **50** to **51**, and a mixture of products was obtained in 70% yield. The formation of a mixture is likely to be a consequence of the lability of the conjugated iodide, as independently corroborated upon treating **52** with a solution of iodine in CH_2Cl_2.

Other electrophiles can be envisaged to function as coupling partners. Although unprecedented in Stille coupling reactions,[56] high regioselectivity has been described for the Suzuki reaction[57] of boronic acids and alkenyl gem-dibromides. We therefore set out to explore the reactivity of the gem-dibromide **59** derived from C_{15}-aldehyde **58**,[58] with alkenyl stannane **31**. However, the coupling product was not detected even after heating the mixture for several hours up to 100 °C. Dibromide **59** also coupled sluggishly to the more reactive[59] alcohol derivative **32** to afford, after 3 h at 80 °C, a retinoid later identified as the known compound 11,12-didehydroretinol **60**,[10b] together with recovered **59** (56% yield). The formation of alkynes from gem-dibromides has been described,[60] and a stannane-induced elimination followed by coupling of the resulting alkynyl bromide with the stannane has been proposed to account for its formation. Even lower reactivity was observed with either **31** or **32** and gem-diiodide **61**, prepared by condensation of **58** and the ylide derived from phosphonium salt $(PPh_3)CHI_2I$ (3 equiv) and *n*-BuLi in THF at 0 °C in 58% yield, even after heating to 100 °C (Scheme 10).[61]

Scheme 10[a]



[a] (a) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 74%. (b) *i.* $(Ph_3PCHI_2)^+I^-$ (3 equiv), *n*-BuLi, THF, 0 °C; *ii.* aldehyde **58**, THF, 0 -> 25 °C, 58%.

Summary

From the above findings, it has been demonstrated that retinoids can be obtained by Stille coupling reactions according to a variety of single-bond forming processes. Whereas the first choice for the location of the stannane and the electrophile was dictated by availability of starting materials, we have also explored the feasibility of the exchange in the functionalization of the Stille coupling partners. The inversion of functionality, which has been used by some authors in inefficient (due to homocoupling and/or low yields) Stille coupling, has sometimes provided an easy alternative to particularly sluggish coupling reactions.[62]
The scope and limitations of each alternative are summarized below.

A) C6-C7 bond formation

Since both components are easily prepared, this route is highly versatile, as has been shown for ring- and side-chain desmethylated retinoids. Tetraenyl stannanes are moderately stable if kept under appropriate conditions as required in retinoid synthesis. However, for sterically hindered triflates high reaction temperatures are required, with erosion in yield due to stannane homocoupling.

B) *C8-C9 bond formation*

Moderate temperatures (50 °C) are needed for the coupling of dienyl iodide **27** and trienyl stannane **30**, which might be an advantage in the preparation of more labile *cis* isomers. However, the preparation of electrophile **27** is limited by the low reactivity of β-cyclocitral (**25**). The formation of the cyclic double bond can be deferred to the last step of an efficient synthesis of retinoids involving coupling of alkenyl stannane **37** and trienyl iodide **35**.

C) C10-C11 bond formation

Regio- and stereoselective preparation of trienyl iodide **41a** and dienyl stannane **17a** are straightforward. The sequence also allows for the preparation of side-chain desmethylated analogs. One drawback is that temperatures of 80 °C are required for the less reactive substrates, which limits its applicability for sensitive retinoids. Although trienyl triflate **46** is more reactive and couples with high efficiency, its preparation suffers from low yields.

D) C12-C13 bond formation

Coupling of **52** and **57** occurs in good yield at room temperature, showing that electrophile **57** is not sensitive to steric hindrance by the geminal methyl group. Additionally, tetraenyl stannane **52** could be used in the parallel preparation of 13-*cis*-retinoids. The main limitation of this approach is the long sequence needed in the preparation of **52**.

From our study, general trends for the application of the Stille coupling to the preparation of conjugated polyenes can be highlighted, despite the fact that the terpenoid-type substitution of the side chain further complicates the analysis of their reactivity. The choice of unhindered coupling partners is clearly of the utmost

importance. We have shown that the reactivity of cycloalkenyl triflates such as **18** is a function of the steric hindrance in the vicinity of the electrophile.[18] The considerable rate differences between cycloalkenyl triflates that differ in their steric bulk are translated into coupling temperatures ranging from 80 °C for **18** to 25 °C for the unsubstituted cyclohexenyl triflate.[18] On the other hand, the coupling of the same triflate **18** to a variety of stannanes (Table 2) exhibited the retarding effect of methyl substituents at the stannane, which might also be of steric origin. The reluctance of cycloalkenyl stannane **20** to react with alkenyl iodides provides further evidence of the importance of steric effects on the coupling of stannanes.[63] Although the rationale for the "appropriate matching" of functionalities appears ill-defined,[62] we have found that electron-deficient electrophiles (such as iodide **57**) couple to unhindered stannnanes (**52**) at ambient temperature. On increasing the distance between the iodine and the ester group, higher temperatures are needed to induce the coupling (i.e. 50 °C for **47** + **24**, and 60 °C for the coupling of **35** and **37**) although both steric and electronic effects are acting simultaneously. For the remaining series of dienyl and trienyl fragments the trends are less defined, although the absence of methyl substituents on the side chain of both coupling partners translates into higher reactivities (see Table 3).

In summary, the exploration of single bond-forming reactions of the retinoid side chain by Stille coupling (A through D, Scheme 2) led to the elucidation of appropriately matched components for every bond considered. Moreover, synthetic schemes for accessing a variety of alkenyl stannanes ranging from enyl to tetraenyl have been developed. Whereas side-chain substituted stannanes and electrophiles have been used for the preparation of the terpenoid skeleton of retinoids, the desmethylated derivatives might be employed with more confidence in the preparation of unsubstituted conjugated polyenes, given the sensitivity of the Stille coupling to steric effects.

Experimental Section

General. Solvents were dried according to published methods and distilled before use. HPLC grade solvents were used for the HPLC purification. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 μm). Proton (^{1}H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on Bruker WM-250 [250 MHz (63 MHz for ^{13}C)], Bruker AMX-300 [300 MHz (75 MHz for ^{13}C)] and AMX-400 [400 MHz (100 MHz for ^{13}C)] Fourier transform spectrometers, and chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm), benzene (C_6H_6, 7.20 ppm for ^{1}H) or chloroform ($CHCl_3$, 7.24 ppm for ^{1}H and 77.00 ppm for ^{13}C) as internal reference. ^{13}C multiplicities (s, singlet; d, doublet; t, triplet; q, quartet) were assigned with the aid of the DEPT pulse sequence. For large Sn-^{1}H or Sn-^{13}C coupling constants (250-300 Hz), the central signal is associated with two close pairs of satellites corresponding to both ^{117}Sn and ^{119}Sn isotopes. In this case, two different coupling constants are reported. For small (<100 Hz) coupling constants, the two pairs of satellites usually collapse, and only one coupling constant is given. Infrared spectra (IR) were obtained on a MIDAC Prospect Model FT-IR spectrophotometer. Absorptions are recorded in wavenumbers (cm^{-1}). UV spectra were recorded on an HP5989A spectrophotometer using MeOH as solvent. Absorption maxima are reported in nm. Melting points (m.p.) were taken on a Kofler apparatus and are uncorrected. Low-resolution mass spectra were taken on an HP59970 instrument operating at 70 eV. High-resolution

mass spectra were taken on a VG Autospec M instrument. All operations involving synthesis and/or manipulation of retinoids were done under subdued light.

(2*E*,4*E*)-3-Methyl-5-(tri-*n*-butylstannyl)penta-2,4-dien-1-al (15a). General Procedure for Alcohol Oxidations with SO_3·Py. A solution of SO_3·Py (0.48 g, 3.0 mmol) in DMSO (3.3 mL) was added to a solution of alcohol **14a**[26] (0.39 g, 1.0 mmol) and Et_3N (0.42 mL, 3.0 mmol) in CH_2Cl_2 (3.3 mL) at -10 °C. After stirring at 0 °C for 30 min, the reaction mixture was added to a mixture of brine and crushed ice and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with 10% citric acid and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (SiO_2, 94:4:2 hexane/EtOAc/Et_3N) afforded 0.37 g (96%) of **15a** as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.8-1.1 (m, 15H, 3 x CH_3 + 3 x CH_2), 1.2-1.4 (m, 6H, 3 x CH_2), 1.4-1.6 (m, 6H, 3 x CH_2), 2.24 (s, 3H, C_3-CH_3), 5.90 (d, J = 8.2 Hz, 1H, H_2), 6.67 (d, J = 19.3 Hz, $^3J_{Sn-H}$ = 57.7 Hz, 1H, H_4), 7.02 (d, J = 19.3 Hz, $^2J_{Sn-H}$ = 59.0 Hz, 1H, H_5), 10.14 (d, J = 8.2 Hz, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1 (t, $^1J_{Sn-C}$ = 347.8/333.2 Hz, 3x), 12.8 (q), 14.0 (q, 3x), 27.6 (t, $^2J_{Sn-C}$ = 55.1 Hz, 3x), 29.4 (t, $^3J_{Sn-C}$ = 21.1 Hz, 3x), 129.5 (d), 142.0 (d, $^1J_{Sn-C}$ = 336.3 Hz, C_5), 149.1 (d), 154.8 (s, C_3), 192.6 (d, C_1) ppm; IR (NaCl) ν 2966 (s, C-H), 2922 (s, C-H), 2857 (s, C-H), 1668 (s, C=O), 1600 (w, C=C), 1453 (w), 1197 (m), 1113 (m), 991 (m), 870 (m), 687 (m) cm^{-1}; MS (EI$^+$) *m/z* (%) 329 (85), 328 (31), 327 (62), 325 (36), 273 (44), 271 (33), 217 (71), 216 (25), 215 (58), 213 (35), 137 (29), 120 (35), 95 ([M - ^{120}SnBu$_3$]$^+$, 100); HRMS (EI$^+$) calcd for $C_{18}H_{34}O^{120}Sn$ 386.1632, found 386.1618.

(2*E*,4*E*)-5-(Tri-*n*-butylstannyl)penta-2,4-dien-1-al (15b). Following the general procedure described above, aldehyde **15b** (0.35 g, 70%) was isolated as a yellow oil, starting from alcohol **14b** (0.5 g, 1.34 mmol). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.8-1.2 (m, 15H, 3 x CH_3 + 3 x CH_2), 1.2-1.4 (m, 6H, 3 x CH_2), 1.4-1.6 (m, 6H, 3 x CH_2), 6.06 (dd, J = 15.0, 8.0 Hz, 1H, H_2), 6.79 (dd, J = 18.8, 10.2 Hz, $^3J_{Sn-H}$ = 53.3 Hz, 1H, H_4), 7.00 (dd, J = 15.3, 10.2 Hz, 1H, H_3), 7.10 (d, J = 18.8 Hz, $^2J_{Sn-H}$ = 60.7 Hz, 1H, H_5), 9.56 (d, J = 8.0 Hz, 1H, CHO) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6 (t, $^1J_{Sn-C}$ = 349.2/330.0 Hz, 3x), 13.6 (q, 3x), 27.2 (t, $^2J_{Sn-C}$ = 54.8 Hz, 3x), 29.0 (t, $^3J_{Sn-C}$ = 20.3 Hz, 3x), 130.1 (d), 144.3 (d), 151.5 (d, $^1J_{Sn-C}$ = 325.5/310.3 Hz, C_5), 153.6 (d, $^2J_{Sn-C}$ = 67.8 Hz, C_4), 194.5 (d, C_1) ppm; MS (EI$^+$) *m/z* (%) 315 ([M - Bu]$^+$, 88), 314 (31), 313 (64), 311 (36), 259 (66), 257 (49), 255 (29), 203 ([M - Bu$_3$]$^+$, 100), 202 (38), 201 (84), 200 (33), 199 (52), 173 (26), 121 (47), 119 (39), 81 ([M - SnBu$_3$]$^+$, 76); HRMS (EI$^+$) calcd for $C_{17}H_{32}O^{120}Sn$ 372.1475, found 372.1483.

Ethyl (2*E*,4*E*,6*E*,8*E*)-7-Methyl-9-(tri-*n*-butylstannyl)nona-2,4,6,8-tetraenoate (12b). General Procedure for the HWE Reaction with LiHMDS. To a cooled (-10 °C) solution of phosphonate **16b** (0.21 g, 0.83 mmol) in THF (25 mL) was added LiHMDS (1 M in THF, 0.9 mL, 0.87 mmol). After stirring for 5 min, it was cooled down to -60 °C and HMPA (0.3 mL, 1.7 mmol) was added. The mixture was stirred at -60 °C for an additional 10 min, it was then cooled to -78 °C, and a solution of stannane **15a** (0.19 g, 0.46 mmol) in THF (0.5 mL) was added. After stirring the resulting mixture at -78 °C for 1 h, it was allowed to reach -20 °C, saturated aqueous NH_4Cl was added and the reaction mixture was extracted with Et_2O. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (SiO_2, 93:5:2 hexane/EtOAc/Et_3N) to afford 0.20 g (90%) of **12b** as a yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 0.93 (t, J = 7.3 Hz, 9H, 3 x CH_3), 0.9-1.1 (m, 9H, $CO_2CH_2C\underline{H}_3$ + 3 x CH_2), 1.3-1.5 (m, 6H, 3 x CH_2), 1.5-1.7 (m, 6H, 3 x CH_2), 1.69 (s, 3H, C_7-CH_3), 4.09 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.92 (d, J = 15.1 Hz, 1H, H_2), 6.00 (d, J = 11.5 Hz, 1H, H_6), 6.04 (dd, J = 14.5, 11.5 Hz, 1H, H_4), 6.55 (d, J = 19.2 Hz, $^2J_{Sn-H}$ = 67.4 Hz, 1H, H_9), 6.57 (dd, J = 14.5, 11.5 Hz, 1H, H_5), 6.82 (d, J = 19.2 Hz, $^3J_{Sn-H}$ = 63.0 Hz, 1H, H_8), 7.54 (dd, J = 15.1, 11.5 Hz, 1H, H_3) ppm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 9H, 3 x CH_3), 0.9-1.0 (m, 6H, 3 x CH_2), 1.2-1.4 (m, 9H, $CO_2CH_2C\underline{H}_3$ + 3 x CH_2), 1.4-1.6 (m, 6H, 3 x CH_2), 1.93 (s, 3H, C_7-CH_3), 4.21 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.87

(d, J = 15.3 Hz, 1H, H_2), 6.15 (d, J = 11.7 Hz, 1H, H_6), 6.38 (dd, J = 14.6, 11.4 Hz, 1H, H_4), 6.48 (d, J = 19.2 Hz, $^2J_{Sn-H}$ = 63.6 Hz, 1H, H_9), 6.63 (d, J = 19.2 Hz, $^3J_{Sn-H}$ = 61.1 Hz, 1H, H_8), 6.94 (dd, J = 15.1, 11.7 Hz, 1H, H_5), 7.39 (dd, J = 15.1, 11.4 Hz, 1H, H_3) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ9.9 (t, $^1J_{Sn-C}$ = 343.3/328.1 Hz, 3x), 12.3 (q), 13.9 (q, 3x), 14.3 (q), 27.7 (t, $^2J_{Sn-C}$ = 53.4 Hz, 3x), 29.5 (t, $^3J_{Sn-C}$ = 20.5 Hz, 3x), 60.1 (t, $CO_2\underline{C}H_2CH_3$), 121.5 (d), 131.0 (d), 131.2 (d), 131.3 (d, $^1J_{Sn-C}$ = 381.5/364.8 Hz, C_9), 137.1 (d), 140.7 (s, C_7), 144.8 (d, $^2J_{Sn-C}$ = 93.6 Hz, C_8), 150.9 (d), 166.7 (s, C_1) ppm; IR (NaCl) ν 2956 (s, C-H), 2926 (s, C-H), 2871 (m, C-H), 2853 (m, C-H), 1712 (s, C=O), 1623 (m), 1597 (m), 1546 (w), 1463 (w), 1367 (w), 1314 (m), 1243 (s), 1166 (w), 1132 (s), 1043 (w), 997 (m) cm^{-1}; UV (MeOH) λ_{max} (ε) 344 (24100) nm; MS (FAB$^+$) m/z (%) 425 ([M - Bu]$^+$, 86), 424 (36), 423 (66), 422 (28), 421 (37), 291 (100), 290 (35), 289 (79), 288 (30), 287 (47), 235 (43), 233 (34), 231 (21); HRMS (FAB$^+$) calcd for $C_{20}H_{33}O_2{}^{120}Sn$ 425.1503, found 425.1495.

Ethyl (2*E*,4*E*,6*E*,8*E*)-3-Methyl-9-(tri-*n*-butylstannyl)nona-2,4,6,8-tetraenoate (12c). General Procedure for the HWE Reaction with *n*-BuLi. To a cooled (0 °C) solution of phosphonate **16a** (0.71 g, 2.7 mmol) in THF (2.7 mL) was added DMPU (0.67 mL, 5.55 mmol), followed by *n*-BuLi (2.36 M in hexanes, 1.1 mL, 2.60 mmol). After stirring for 20 min, the mixture was cooled to -78 °C. A solution of aldehyde **15b** (0.56 g, 1.5 mmol) in THF (2.7 mL) was slowly added, and the reaction mixture was stirred at -78 °C for 3 h, after which time it was allowed to warm up to 0 °C. Saturated aqueous NH_4Cl was added and the reaction mixture was extracted with Et_2O. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (SiO_2, 93:5:2 hexane/EtOAc/Et_3N) afforded 0.57 g (79%) of **12c** as a yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ1.04 (t, J = 7.3 Hz, 9H, 3 x CH_3), 1.1-1.2 (m, 9H, $CO_2CH_2C\underline{H}_3$ + 3 x CH_2), 1.4-1.5 (m, 6H, 3 x CH_2), 1.6-1.8 (m, 6H, 3 x CH_2), 2.46 (s, 3H, C_3-CH_3), 4.15 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.99 (s, 1H, H_2), 6.15 (dd, J = 14.8, 10.9 Hz, 1H, H_6), 6.17 (d, J = 15.1 Hz, 1H, H_4), 6.34 (dd, J = 14.8, 10.1 Hz, 1H, H_7), 6.53 (dd, J = 15.1, 10.9 Hz, 1H, H_5), 6.62 (d, J = 18.7 Hz, $^2J_{Sn-H}$ = 66.4 Hz, 1H, H_9), 6.88 (dd, J = 18.4, 10.1 Hz, $^3J_{Sn-H}$ = 57.4 Hz, 1H, H_8) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ9.9 (t, $^1J_{Sn-C}$ = 344.0/328.8 Hz, 3x), 13.7 (q), 14.0 (q, 3x), 14.4 (q), 27.7 (t, $^2J_{Sn-C}$ = 54.8 Hz, 3x), 29.6 (t, $^3J_{Sn-C}$ = 24.0 Hz, 3x), 59.6 (t, $CO_2\underline{C}H_2CH_3$), 120.0 (d), 131.9 (d, $^2J_{Sn-C}$ = 174.8 Hz, C_8), 134.8 (d), 136.6 (d, $^3J_{Sn-C}$ = 87.4 Hz, C_7), 137.4 (d, $^1J_{Sn-C}$ = 376.6/360.0 Hz, C_9), 138.7 (d, $^3J_{Sn-C}$ = 73.5 Hz, C_7), 147.3 (d), 152.2 (s, C_3), 166.7 (s, C_1) ppm; IR (NaCl) ν 2957 (s, C-H), 2927 (s, C-H), 2872 (m, C-H), 2853 (m, C-H), 1712 (s, C=O), 1614 (m), 1589 (m), 1463 (w), 1352 (w), 1241 (m), 1154 (f), 1046 (w), 1003 (m) cm^{-1}; UV (MeOH) λ_{max} (ε) 336 (18900) nm; MS (FAB$^+$) m/z (%) 425 ([M - Bu]$^+$, 100), 424 (42), 423 (78), 422 (32), 421 (44), 291 (100), 290 (35), 289 (79), 288 (30), 287 (47), 235 (58), 233 (46), 231 (28); HRMS (FAB$^+$) calcd for $C_{20}H_{33}O_2{}^{120}Sn$ 425.1502, found 425.1502; calcd for $C_{20}H_{33}O_2{}^{116}Sn$ 421.1498, found 421.1502.

Ethyl (2*E*,4*E*,6*E*,8*E*)-9-(Tri-*n*-butylstannyl)nona-2,4,6,8-tetraenoate (12d). Following the general procedure described above, a mixture of phosphonate **16b** (0.34 g, 1.35 mmol) and HMPA (0.5 mL, 2.77 mmol) in THF (37 mL), was treated with LiHMDS (1 M in hexanes, 1.3 mL, 1.31 mmol) followed by a solution of stannane **15b** (0.28 g, 0.75 mmol) in THF (1 mL). Purification by chromatography (SiO_2, 93:5:2 hexane/EtOAc/Et_3N) afforded 0.16 g (47%) of **12d** as a yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 0.8-1.1 (m, 18H, $CO_2CH_2C\underline{H}_3$ + 3 x CH_3 + 3 x CH_2), 1.2-1.4 (m, 6H, 3 x CH_2), 1.5-1.7 (m, 6H, 3 x CH_2), 4.07 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.90 (d, J = 15.2 Hz, 1H, H_2), 5.97 (m, 2H, H_4 + H_6), 6.17 (m, 2H, H_5 + H_7), 6.48 (d, J = 18.6 Hz, 1H, H_9), 6.73 (dd, J = 18.6, 10.1 Hz, 1H, H_8), 7.48 (dd, J = 15.2, 11.3 Hz, 1H, H_3) ppm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.8-1.0 (m, 15H, 3 x CH_3 + 3 x CH_2), 1.2-1.4 (m, 9H, $CO_2CH_2C\underline{H}_3$ + 3 x CH_2), 1.4-1.6 (m, 6H, 3 x CH_2), 4.21 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.87 (d, J = 12.3 Hz, 1H, H_2), 6.2-6.4 (m, 3H, H_4 + H_6 + H_7), 6.47 (d, J = 18.7 Hz, 1H, H_9), 6.5-6.7 (m, 2H, H_5 + H_8), 7.33 (dd, J = 15.1, 11.4 Hz, 1H, H_3) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 9.8 (t, $^1J_{Sn-C}$ = 344.3/329.0 Hz, 3x), 14.0 (q, 3x), 14.4 (q, $CO_2CH_2\underline{C}H_3$), 27.7 (t, $^2J_{Sn-C}$ = 33.6 Hz, 3x), 29.5 (t,

$^3J_{Sn-C}$ = 19.8 Hz, 3x), 60.1 (t, $CO_2\underline{C}H_2CH_3$), 121.4 (d), 130.9 (d), 131.3 (d), 138.5 (d, $^1J_{Sn-C}$ = 373.1/356.6 Hz, C_9), 139.4 (d, J_{Sn-C} = 75.6/72.4 Hz, C_8 or C_7), 140.7 (d), 144.4 (d), 147.1 (d), 166.6 (s, C_1) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ9.6 (t, $^1J_{Sn-C}$ = 346.1/330.8 Hz, 3x), 13.7 (q, 3x), 14.3 (q, $CO_2CH_2\underline{C}H_3$), 27.2 (t, $^2J_{Sn-C}$ = 55.4/53.8 Hz, 3x), 29.1 (t, $^3J_{Sn-C}$ = 20.8 Hz, 3x), 60.2 (t, $CO_2\underline{C}H_2CH_3$), 120.6 (d), 130.2 (d), 130.5 (d), 139.5 (d, $^2J_{Sn-C}$ = 74.7 Hz, C_8), 139.6 (d, $^1J_{Sn-C}$ = 365.5/349.3 Hz, C_9), 140.8 (d), 144.3 (d), 146.3 (d), 167.1 (s, C_1) ppm; IR (NaCl) ν 2957 (s, C-H), 2927 (s, C-H), 2872 (m), 2853 (m), 1713 (s, C=O), 1625 (m), 1463 (w), 1367 (w), 1299 (m), 1261 (m), 1130 (s), 1009 (s) cm^{-1}; UV (MeOH) λ_{max} (ε) 336 (15900) nm; MS (FAB$^+$) *m/z* (%) 411 (89), 410 (37), 409 (69), 408 (29), 407 (39), 291 (76), 290 (27), 289 (62), 287 (38), 251 (25), 235 (100), 234 (35), 233 (81), 232 (30), 231 (50); HRMS (FAB$^+$) calcd for $C_{19}H_{31}O_2{}^{120}Sn$ 411.1346, found 411.1364.

Ethyl 13-Desmethylretinoate (11b). General Procedure for Stille Reactions. A solution of $Pd_2(dba)_3$ (5.0 mg, 0.006 mmol) in NMP (2.5 mL) was treated with $AsPh_3$ (13.5 mg, 0.044 mmol). After stirring for 5 min, a solution of triflate **18** (60 mg, 0.22 mmol) in NMP (0.5 mL) was added and the mixture was stirred for 10 min. A solution of stannane **12b** (96 mg, 0.2 mmol) in NMP (0.5 mL) was then added, and the resulting mixture was stirred at 70 °C for 2 h. After cooling down to 25 °C, a saturated aqueous KF solution (3 mL) was added and the mixture was stirred for 30 min. It was then extracted with Et_2O, the combined organic extracts were washed with H_2O and saturated aqueous KF, dried ($MgSO_4$), and evaporated. Purification of the residue by chromatography (SiO_2, 98:2 hexane/ EtOAc) afforded 47 mg (75%) of **11b** as a yellow oil, and 11 mg (30%) of diethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-7,12-dimethyloctadeca-2,4,6,8,10,12,14,16-octaene-1,18-dioate **19b** as a red solid (mp: 124-127 °C, EtOAc). Data for **11b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 6H, C_1-2CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.3-1.7 (m, 4H, $2H_2$ + $2H_3$), 1.72 (s, 3H, C_5-CH_3), 1.99 (s, 3H, C_9-CH_3), 2.0-2.1 (m, 2H, $2H_4$), 4.21 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.85 (d, *J* = 15.2 Hz, 1H, H_{14}), 6.13 (d, *J* = 15.7 Hz, 2H, H_8 + H_{12}), 6.2-6.4 (m, 2H, H_7 + H_{10}), 6.95 (dd, *J* = 14.5, 11.8 Hz, 1H, H_{11}), 7.39 (dd, *J* = 15.2, 11.5 Hz, 1H, H_{13}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (q), 14.3 (q), 19.2 (t), 21.7 (q), 28.9 (q, 2x), 33.1 (t), 34.2 (s), 39.5 (t), 60.2 (t, $CO_2\underline{C}H_2CH_3$), 119.7 (d), 129.1 (d), 129.3 (d), 129.4 (d), 130.2 (s), 137.1 (d), 137.2 (d), 137.6 (s), 140.7 (s), 144.9 (d), 167.3 (s, C_{15}) ppm; MS (EI$^+$) *m/z* (%) 314 (M$^+$, 100), 171 (15), 157 (16), 145 (15), 119 (15), 105 (13), 91 (21), 69 (21); HRMS (EI$^+$) calcd for $C_{21}H_{30}O_2$ 314.2246, found 314.2250. Data for **19b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 6H, 2 x $CO_2CH_2C\underline{H}_3$), 1.98 (s, 6H, C_7-CH_3 + C_{12}-CH_3), 4.22 (q, *J* = 7.1 Hz, 4H, 2 x $CO_2C\underline{H}_2CH_3$), 5.89 (d, *J* = 15.2 Hz, 2H, H_2 + H_{17}), 6.23 (d, *J* = 11.8 Hz, 2H, H_6 + H_{13}), 6.3-6.5 (m, 6H, H_4 + H_8 + H_9 + H_{10} + H_{11} + H_{15}), 6.93 (dd, *J* = 14.5, 11.8 Hz, 2H, H_5 + H_{14}), 7.39 (dd, *J* = 15.2, 11.5 Hz, 2H, H_3 + H_{16}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (q, 2x), 14.3 (q, 2x), 60.2 (t, 2 x $CO_2\underline{C}H_2CH_3$), 120.5 (d, 2x), 130.6 (d, 2x), 130.9 (d, 2x), 131.5 (d, 2x), 136.8 (d, 2x), 137.9 (d, 2x), 140.3 (s, C_7 + C_{12}), 144.6 (d, 2x), 167.2 (s, C_1 + C_{18}) ppm; IR (NaCl) ν 3023 (w, C-H), 2961 (m, C-H), 2925 (m, C-H), 2854 (w, C-H), 1703 (s, C=O), 1617 (m), 1572 (w), 1305 (w), 1247 (m), 1133 (m), 1037 (w) cm^{-1}; MS (EI$^+$) *m/z* (%) 383 ([M + 1]$^+$, 27), 382 (M$^+$, 100), 278 (20), 277 (46), 199 (27), 197 (23), 195 (22), 143 (23), 131 (29), 129 (20), 105 (23), 91 (34), 85 (21), 71 (29); HRMS (EI$^+$) calcd for $C_{24}H_{30}O_4$ 382.2144, found 382.2152.

Ethyl 9-Desmethylretinoate (11c). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (13 mg, 0.014 mmol), $AsPh_3$ (34 mg, 0.11 mmol), triflate **18** (150 mg, 0.55 mmol), and stannane **12c** (241 mg, 0.50 mmol) in NMP (7.5 mL) was stirred at 50 °C for 2 h, to afford, after purification by chromatography (SiO_2, 98:2 hexane/EtOAc), 0.14 g (87%) of **11c** as a yellow oil and 21 mg (22%) of diethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-3,16-dimethyloctadeca-2,4,6,8,10,12,14,16-octaene-1,18-dioate **19c** as a red solid (mp: 135-137 °C, EtOAc). Data for **11c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 6H, C_1-2CH_3), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.4-1.7 (m, 4H, $2H_2$ + $2H_3$), 1.73 (s, 3H, C_5-CH_3), 2.0-2.1 (m, 2H, $2H_4$), 2.32 (s, 3H, C_{13}-CH_3), 4.17 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.76 (s, 1H, H_{14}), 6.16 (dd, *J* = 15.6, 10.5 Hz, 1H, H_8), 6.2-6.4 (m, 3H, H_7 + H_{10} + H_{12}), 6.47 (dd, *J* = 14.8, 10.5 Hz, 1H, H_9), 6.68 (dd, *J* = 15.3, 10.9

Hz, 1H, H_{11}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (q), 14.3 (q), 19.1 (t), 20.9 (q), 28.9 (q, 2x), 33.3 (t), 34.1 (s, C_1), 39.7 (t), 59.6 (t, $CO_2\underline{C}H_2CH_3$), 118.7 (d), 130.4 (s), 131.2 (d), 132.9 (d), 133.9 (d), 134.7 (d), 135.0 (d), 137.3 (s), 137.4 (d), 152.4 (s), 167.1 (s, C_{15}) ppm; IR (NaCl) ν 2930 (m, C-H), 2866 (m, C-H), 1708 (s, C=O), 1589 (m), 1446 (w), 1366 (w), 1238 (m), 1151 (s) cm^{-1}; MS (EI^+) *m/z* (%) 314 (M^+, 100), 299 (26), 241 (22), 171 (20), 147 (15), 139 (15), 105 (23), 91 (20); HRMS (EI^+) calcd for $C_{21}H_{30}O_2$ 314.2246, found 314.2246. Data for **19c**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 6H, 2 x $CO_2CH_2C\underline{H}_3$), 2.32 (d, *J* = 0.6 Hz, 6H, C_3-CH_3 + C_{16}-CH_3), 4.18 (q, *J* = 7.1 Hz, 4H, 2 x $CO_2C\underline{H}_2CH_3$), 5.79 (s, 2H, H_2 + H_{17}), 6.30 (d, *J* = 15.2 Hz, 2H, H_4 + H_{15}), 6.3-6.5 (m, 8H, H_6 + H_7 + H_8 + H_9 + H_{10} + H_{11} + H_{12} + H_{13}), 6.68 (dd, *J* = 15.2, 10.6 Hz, 2H, H_5 + H_{14}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (q, 2x), 14.3 (q, 2x), 59.7 (t, 2 x $CO_2\underline{C}H_2CH_3$), 119.5 (d, 2x), 133.2 (d, 2x), 133.9 (d, 2x), 134.6 (d, 2x), 134.7 (d, 2x), 136.1 (d, 2x), 136.2 (d, 2x), 152.1 (s, C_3 + C_{16}), 167.1 (s, C_1 + C_{18}) ppm; IR (NaCl) ν 2983 (w, C-H), 1701 (s, C=O), 1606 (w), 1443 (w), 1359 (w), 1240 (m), 1153 (s), 1046 (w), 1006 (s), 882 (w) cm^{-1}.

Ethyl 9,13-Bisdesmethylretinoate (11d). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (13 mg, 0.014 mmol), $AsPh_3$ (34 mg, 0.11 mmol), triflate **18** (0.15 g, 0.55 mmol), and stannane **12d** (0.23 g, 0.50 mmol) in NMP (7.5 mL) was stirred at 50 °C for 2 h to afford, after purification by chromatography (SiO_2, 98:2 hexane/EtOAc), 0.13 g (85%) of **11d** as a yellow oil and 20 mg (22%) of diethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-octadeca-2,4,6,8,10,12,14,16-octaene-1,18-dioate **19d** as a red solid (mp: 110-113 °C, EtOAc). Data for **11d**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 6H, C_1-$2CH_3$), 1.30 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.4-1.7 (m, 4H, $2H_2$ + $2H_3$), 1.74 (s, 3H, C_5-CH_3), 2.03 (t, *J* = 6.1 Hz, 2H, $2H_4$), 4.21 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.85 (d, *J* = 15.2 Hz, 1H, H_{14}), 6.16 (dd, *J* = 15.6, 10.5 Hz, 1H, H_8), 6.2-6.4 (m, 3H, H_7 + H_{10} + H_{12}), 6.48 (dd, *J* = 14.7, 10.6 Hz, 1H, H_9), 6.62 (dd, *J* = 14.6, 11.2 Hz, 1H, H_{11}), 7.33 (dd, *J* = 15.2, 11.4 Hz, 1H, H_{13}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (q), 19.1 (t), 21.7 (q), 28.9 (q, 2x), 33.3 (t), 34.1 (s), 39.7 (t), 60.2 (t, $CO_2\underline{C}H_2CH_3$), 120.0 (d), 129.0 (d), 129.9 (d), 131.6 (s), 132.7 (d), 134.8 (d), 137.4 (s), 138.4 (d), 141.1 (d), 144.6 (d), 167.2 (s, C_{15}) ppm; IR (NaCl) ν 2929 (s, C-H), 2866 (s, C-H), 1711 (s, C=O), 1624 (m), 1589 (s), 1458 (m), 1304 (s), 1240 (s), 1141 (s), 1007 (s), 757 (m) cm^{-1}; MS (EI^+) *m/z* (%) 300 (M^+, 100), 285 (52), 227 (17), 187 (16), 159 (20), 157 (20), 145 (19), 129 (15), 128 (15), 91 (30); HRMS (EI^+) calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2087.

(2*E*,4*E*)-5-Iodo-3-methylpenta-2,4-dienal (23). General Procedure for Alcohol Oxidations with MnO_2. To a solution of alcohol **22** (0.15 g, 0.67 mmol) in CH_2Cl_2 (5 mL) was added MnO_2 (1.05 g, 12.06 mmol). After stirring the reaction mixture at 25 °C for 2 h, it was filtered through a Celite® pad. Evaporation of the solvent and purification of the residue by chromatography (SiO_2, 80:20 hexane/ethyl acetate) yielded 0.13 g (89%) of aldehyde **23**, which must be used immediately, due to its instability. ^1H-NMR (400 MHz, C_6D_6) δ 1.25 (d, *J* = 0.7 Hz, 3H, C_3-CH_3), 5.43 (d, *J* = 7.6 Hz, 1H, H_2), 6.23 (d, *J* = 14.8 Hz, 1H, H_5), 6.58 (d, *J* = 14.8 Hz, 1H, H_4), 9.72 (d, *J* = 7.6 Hz, 1H, H_1).

Methyl (2*E*,4*E*)-5-Iodo-3-methylpenta-2,4-dienoate (24). General Procedure for the Tin/Iodine Exchange Reaction. To a cooled (0 °C) solution of stannane **17a** (0.41 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was slowly added a solution of I_2 (0.25 g, 1.0 mmol) in CH_2Cl_2 (8 mL) and the reaction mixture was stirred at 0 °C for 10 min. Saturated aqueous KF (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL) were added and the mixture was stirred at 25 °C for 30 min, and then extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ and H_2O, dried ($MgSO_4$) and evaporated. Purification of the residue by chromatography (SiO_2, 95:5 hexane/EtOAc) afforded 0.22 g (90%) of dienyliodide **24**. ^1H-NMR (400 MHz, $CDCl_3$) δ 2.22 (d, *J* = 1.2 Hz, 3H, C_3-CH_3), 3.69 (s, 3H, $CO_2C\underline{H}_3$), 5.72 (s, 1H, H_2), 6.87 (d, *J* = 14.7 Hz, 1H, H_5), 7.08 (d, *J* = 14.7 Hz, 1H, H_4); ^{13}CNMR (100 MHz, $CDCl_3$) δ 13.2 (q, C_3-CH_3), 51.2 (q, $CO_2\underline{C}H_3$), 84.4 (d), 119.8 (d), 148.2 (d), 151.1 (s, C_3), 166.9 (s, CO).

Pinacol [(*E*)-2-(2,6,6-Trimethylcyclohex-1-en-1-yl)ethen-1-yl]borane (29). General Procedure for the Preparation of Pinacol Boranes. $BH_3{\cdot}SMe_2$ (1.8 mL, 19 mmol) was slowly added to a cooled (0 °C) solution of pinacol (2.25 g, 19 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at this temperature for 1 h and at 25 °C for an additional 1 h. A solution of 2-ethynyl-1,3,3-trimethylcyclohex-1-ene **28** (0.47 g, 3.2 mmol) in CH_2Cl_2 (0.5 mL) was slowly added at 0 °C, and the reaction mixture was stirred at 25 °C for 1 h and at 50 °C for an additional 5 h. After cooling down to 25 °C, Et_2O and saturated aqueous NH_4Cl were added. The organic layer was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (SiO_2, 95:5 hexane/EtOAc) afforded, in order of elution, 0.22 g of starting material **28** and 0.22 g (25% yield, 46% conversion) of **29** as a red oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 6H, C_6-2CH_3), 1.29 (s, 12H, -OC$(CH_3)_2$C$(CH_3)_2$O-), 1.4-1.5 (m, 2H, $2H_4$·), 1.5-1.7 (m, 2H, $2H_5$·), 1.71 (s, 3H, C_2-CH_3), 2.00 (t, J = 6.1 Hz, 2H, $2H_3$·), 5.42 (d, J = 18.6 Hz, 1H, H_1), 7.01 (d, J = 18.6 Hz, 1H, H_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3 (t), 21.6 (q), 24.8 (q, 4x, -OC$(\underline{C}H_3)_2$C$(\underline{C}H_3)_2$O-), 28.8 (q, 2x, C_6-2$\underline{C}H_3$), 33.1 (t), 33.8 (s, C_6·), 39.8 (t), 82.9 (s, 2x, -O$\underline{C}(CH_3)_2\underline{C}(CH_3)_2$O-), 130.9 (s), 139.2 (s), 149.5 (d, 2x, C_1 + C_2) ppm; IR (NaCl) ν 2929 (s, C-H), 2866 (s, C-H), 1617 (s), 1459 (m), 1350 (s), 1320 (s), 1267 (m), 1212 (m), 1146 (s), 970 (m) cm^{-1}; MS (EI$^+$) *m/z* (%) 276 (M^+, 46), 261 (53), 232 (26), 220 (33), 176 (15), 161 (100), 160 (26), 133 (22), 120 (13), 101 (31), 91 (15), 84 (52), 83 (24); HRMS (EI$^+$) calcd for $C_{17}H_{29}BO_2$ 276.2261, found 276.2262.

1,3,3-Trimethyl-2-[(*E*)-2-iodoethen-1-yl]cyclohex-1-ene (27). General Procedure for the Boron/Iodine Exchange Reaction. A solution of boronate **29** (0.28 g, 1.0 mmol) in THF (16 mL) was cooled to -78 °C and treated with a suspension of MeONa (0.11 g, 2 mmol) in MeOH (1 mL). After stirring for 20 min, ICl (1.5 M in CH_2Cl_2, 0.7 mL, 1.05 mmol) was slowly added and the mixture was stirred at -78 °C for an additional 1 h. Et_2O was added, the organic layer was separated and washed with 5% aqueous $Na_2S_2O_5$, H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (SiO_2, hexane) to afford 0.18 g (65%) of **27** as a red oil. ^1H NMR (400 MHz, C_6D_6) δ 0.86 (s, 6H, C_3-2CH_3), 1.2-1.4 (m, 4H, $2H_4$ + $2H_5$), 1.46 (d, J = 1.0 Hz, 3H, C_1-CH_3), 1.6-1.7 (m, 2H, $2H_6$), 5.81 (d, J = 14.7 Hz, 1H, H_2·), 6.96 (dd, J = 14.7, 1.0 Hz, 1H, H_1·) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 19.3 (t), 21.5 (q), 28.6 (q, 2x), 32.8 (t), 33.8 (s), 39.3 (t), 78.9 (d, C_2·), 130.7 (s), 139.2 (s), 144.3 (d, C_1·) ppm; IR (NaCl) ν 2928 (s, C-H), 2865 (s, C-H), 1581 (w), 1458 (m), 1361 (w), 1164 (m), 946 (s) cm^{-1}; MS (EI$^+$) *m/z* (%) 276 (M^+, 71), 261 (100), 162 (34), 134 (27), 119 (22), 105 (17), 95 (19), 93 (19), 91 (21), 83 (21), 81 (19), 71 (21), 69 (30); HRMS (EI$^+$) calcd for $C_{11}H_{17}I$ 276.0375, found 276.0371.

(*E*)-3-(Tri-*n*-butylstannyl)but-2-en-1-ol (32). To a cooled (0 °C) suspension of $LiAlH_4$ (0.7 g, 18.5 mmol) in Et_2O (10 mL) was added a solution of **31** (6.5 g, 16.1 mmol) in Et_2O (34 mL). After stirring at 0 °C for 4 h, a 9:1 MeOH/H_2O (20 mL) mixture was added and the temperature was allowed to reach 25 °C. 10% NH_4Cl was then added, and the final mixture was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated. Purification of the residue by chromatography (SiO_2, 79:20:1 hexane/EtOAc/Et_3N) afforded 4.2 g (72%) of **32** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.8-1.0 (m, 15H, 3 x CH_3 + 3 x CH_2), 1.2-1.4 (m, 6H, 3 x CH_2), 1.4-1.6 (m, 6H, 3 x CH_2), 1.89 (app t, J = 0.8 Hz, $^3J_{Sn\text{-}H}$ = 45.1 Hz, 3H, $3H_4$), 4.26 (d, J = 6.1 Hz, 2H, $2H_1$), 5.76 (app tq, J = 6.1, 1.8 Hz, $^3J_{Sn\text{-}H}$ = 67.7 Hz, 1H, H_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5 (t, 3x), 14.1 (q, 3x), 19.8 (q, C_4), 27.8 (t, 3x), 29.5 (t, 3x), 59.3 (t, C_1), 139.6 (d, C_2), 142.5 (s, C_3) ppm; IR (NaCl) ν 3600-3100 (br, O-H), 2922 (s, C-H), 2860 (s), 1456 (w), 1062 (w), 1008 (w) cm^{-1}; MS (EI$^+$) *m/z* (%) 305 ([M - Bu]$^+$, 100), 304 (35), 303 (67), 301 (35), 249 (44), 247 (33), 193 (49), 191 (42), 189 (27), 179 (47), 177 (52), 175 (35), 137 (42), 135 (34), 121 (44), 119 (34).

(*E*)-3-(Tri-*n*-butylstannyl)but-2-enal (33). In accordance to the general procedure described above, alcohol **32** (0.9 g, 2.5 mmol) in CH_2Cl_2 (30 mL) was treated with MnO_2 (3.9 g, 45 mmol) and Na_2CO_3 (4.8 g, 45 mmol) to afford, after purification by chromatography (SiO_2, 94:5:1 hexane/EtOAc/Et_3N), 0.76 g (85%) of **33** as a yellow oil. ^1H NMR (400

MHz, $CDCl_3$) δ 0.90 (m, 9H, 3 x CH_3), 1.00 (t, J = 8.2 Hz, 6H, 3 x CH_2), 1.2-1.4 (m, 6H, 3 x CH_2), 1.4-1.6 (m, 6H, 3 x CH_2), 2.46 (d, J = 1.8 Hz, $^3J_{Sn-H}$ = 43.4 Hz, 3H, $3H_4$), 6.22 (dq, J = 8.0, 1.7 Hz, $^3J_{Sn-H}$ = 59.9 Hz, 1H, H_2), 10.06 (d, J = 8.0 Hz, 1H, H_1) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3 (t, $^1J_{Sn-C}$ = 336.7/321.7 Hz, 3x), 13.5 (q, 3x), 20.6 (q, C_4), 27.2 (t, $^2J_{Sn-C}$ = 57.0/55.3 Hz, 3x), 28.9 (t, $^3J_{Sn-C}$ = 26.8 Hz, 3x), 139.8 (d, $^2J_{Sn-C}$ = 21.4 Hz, C_2), 174.1 (s, C_3), 187.3 (d, $^3J_{Sn-C}$ = 58.6 Hz, C_1) ppm; IR (NaCl) ν 2966 (s, C-H), 2902 (s, C-H), 2857 (s, C-H), 1678 (s, C=O), 1471 (w), 1374 (w), 1155 (w), 1070 (w), 875 (w) cm^{-1}; MS (EI^+) *m/z* (%) 307 (46), 305 (72), 304 (30), 303 ([M - Bu]$^+$, 100), 302 (31), 301 (59), 249 (42), 247 (73), 245 (50), 193 (39), 191 (55), 189 (47), 179 (46), 177 (57), 175 (40), 137 (51), 135 (42), 121 (63), 119 (50), 117 (29); HRMS (FAB$^+$) calcd for $C_{12}H_{23}O^{120}Sn$ 303.0771, found 303.0757.

Ethyl (2*E*,4*E*,6*E*)-3-Methyl-7-(tri-*n*-butylstannyl)octa-2,4,6-trienoate (30). Following the general procedure described above, a mixture of phosphonate **16a** (1.32 g, 5.0 mmol) and DMPU (1.2 mL, 10 mmol) in THF (5 mL) was treated with *n*-BuLi (2.6 M in hexane, 1.8 mL, 4.68 mmol), followed by a solution of stannane **33** (1.0 g, 2.78 mmol) in THF (5 mL) to afford, after purification by chromatography (SiO_2, 93:5:2 hexane/EtOAc/Et_3N), 0.96 g (74%) of **30** as a yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 1.03 (m, 9H, 3 x CH_3), 1.0-1.1 (m, 9H, 3 x CH_2 + $CO_2CH_2C\underline{H}_3$), 1.4-1.6 (m, 6H, 3 x CH_2), 1.6-1.8 (m, 6H, 3 x CH_2), 2.10 (d, J = 1.1 Hz, $^3J_{Sn-H}$ = 47.7 Hz, 3H, $3H_8$), 2.54 (d, J = 0.9 Hz, 3H, C_3-CH_3), 4.15 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 6.02 (s, 1H, H_2), 6.24 (d, J = 15.2 Hz, 1H, H_4), 6.57 (dd, J = 10.7, 1.5 Hz, $^3J_{Sn-H}$ = 64.7 Hz, 1H, H_6), 7.08 (dd, J = 15.2, 10.7 Hz, 1H, H_5) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 9.7 (t, $^1J_{Sn-C}$ = 329.8/316.1 Hz, 3x), 14.0 (q, 3x), 14.1 (q), 14.6 (q), 20.5 (q, $^2J_{Sn-C}$ = 36.8 Hz, C_8), 27.9 (t, $^2J_{Sn-C}$ = 54.6 Hz, 3x), 29.7 (t, $^3J_{Sn-C}$ = 20.7 Hz, 3x), 59.7 (t, $CO_2\underline{C}H_2CH_3$), 120.1 (d), 128.5 (d, $^3J_{Sn-C}$ = 64.0 Hz, C_5), 135.6 (d), 139.7 (d, $^2J_{Sn-C}$ = 30.5 Hz, C_6), 149.5 (s), 153.0 (s), 166.8 (s, C_1) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (t, $^1J_{Sn-C}$ = 371.3/319.2 Hz, 3x), 14.1 (q, 3x), 14.2 (q), 14.7 (q), 20.8 (q), 27.8 (t, $^2J_{Sn-C}$ = 44.8 Hz, 3x), 29.5 (t, $^3J_{Sn-C}$ = 23.0 Hz, 3x), 60.0 (t, $CO_2\underline{C}H_2CH_3$), 119.2 (d), 128.7 (d, $^2J_{Sn-C}$ = 62.8 Hz, C_6), 135.0 (d), 138.9 (d, $^3J_{Sn-C}$ = 30.4 Hz, C_5), 151.1 (s), 153.5 (s), 167.5 (s, C_1) ppm; IR (NaCl) ν 2954 (s, C-H), 2924 (s, C-H), 2863 (m), 1708 (s, C=O), 1611 (m, C=C), 1458 (w), 1246 (m), 1148 (s), 1039 (w), 961 (w) cm^{-1}; MS (EI^+) *m/z* (%) 413 ([M - Bu]$^+$, 100), 412 (40), 411 (74), 410 (30), 409 (41), 357 (35), 301 (44), 299 (34), 179 (89), 177 (94), 176 (31), 175 (65), 165 (69), 163 (67), 161 (35), 137 (38), 135 (57), 133 (81), 121 (85), 120 (45), 119 (80), 118 (34), 117 (40), 107 (53), 105 (58), 91 (44).

Ethyl Retinoate (11a). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (4.3 mg, 0.005 mmol), $AsPh_3$ (11.6 mg, 0.038 mmol), iodide **27** (50 mg, 0.19 mmol), and stannane **30** (98 mg, 0.21 mmol) in NMP (3 mL) was stirred at 50 °C for 3 h. Purification by chromatography (SiO_2, 98:2 hexane/EtOAc) afforded 35 mg (56%) of **11a**[19] as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 6H, C_1-$2CH_3$), 1.29 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.4-1.6 (m, 4H, $2H_2$ + $2H_3$), 1.72 (s, 3H, C_5-CH_3), 2.00 (s, 3H, C_9-CH_3), 2.0-2.1 (m, 2H, $2H_4$), 2.36 (d, J = 1.0 Hz, 3H, C_{13}-CH_3), 4.17 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.78 (s, 1H, H_{14}), 6.14 (d, J = 16.1 Hz, 1H, H_8), 6.15 (d, J = 11.2 Hz, 1H, H_{10}), 6.28 (d, J = 16.1 Hz, 1H, H_7), 6.29 (d, J = 15.0 Hz, 1H, H_{12}), 7.00 (dd, J = 15.0, 11.2 Hz, 1H, H_{11}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (q), 13.7 (q), 14.3 (q), 19.1 (t), 21.8 (q), 28.9 (q, 2x), 33.0 (t), 34.2 (s), 39.4 (t), 59.7 (t, $CO_2\underline{C}H_2CH_3$), 118.5 (d), 128.5 (d), 129.4 (d), 130.0 (s), 130.9 (d), 135.1 (d), 137.2 (d), 137.6 (s), 139.5 (s), 152.8 (s), 167.2 (s, C_{15}) ppm.

Ethyl (2*E*,4*E*,6*E*)-7-Iodo-3-methylocta-2,4,6-trienoate (35). In accordance to the general procedure described above, stannane **30** (0.42 g, 0.9 mmol) in CH_2Cl_2 (7 mL) was treated with a solution of I_2 (0.23 g, 0.9 mmol) in CH_2Cl_2 (9 mL) to yield, after purification by chromatography (SiO_2, 95:5 hexane/EtOAc), 0.27 g (98%) of **35** as a yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 1.04 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.11 (s, 3H, C_3-CH_3), 2.29 (d, J = 1.1 Hz, 3H, $3H_8$), 4.07 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.79 (d, J = 15.2 Hz, 1H, H_4), 5.87 (s, 1H, H_2), 6.27 (dd, J = 15.2, 11.1 Hz, 1H, H_5), 6.67 (d, J = 11.1 Hz, 1H, H_6) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 13.6 (q), 14.4 (q), 28.1 (q), 59.7 (t, $CO_2\underline{C}H_2CH_3$), 101.2 (s),

121.0 (d), 136.2 (d), 140.7 (d), 151.6 (s), 166.5 (s, C_1) ppm; IR (NaCl) ν 2977 (m, C-H), 1703 (s, C=O), 1603 (m), 1581 (w), 1443 (w), 1396 (w), 1365 (w), 1256 (w), 1237 (m), 1153 (s), 1061 (m), 1047 (m), 960 (m), 830 (w) cm^{-1}; MS (EI^+) *m/z* (%) 306 (M^+, 87), 267 (22), 261 (23), 233 (22), 179 (27), 162 (34), 149 (39), 133 (26), 111 (27), 107 (100), 106 (36), 105 (81), 97 (42), 95 (31), 91 (90), 85 (41), 83 (42), 81 (27), 79 (27), 71 (60), 69 (46); HRMS (EI^+) calcd for $C_{11}H_{15}O_2I$ 306.0117, found 306.0116.

1-[(*E*)-2-(Tri-*n*-butylstannyl)ethen-1-yl]-2,6,6-trimethylcyclohexan-1-ol (37). To a solution of propargyl alcohol **36**[35] (0.66 g, 4.0 mmol) and $PdCl_2(PPh_3)_2$ (0.19 g, 0.4 mmol) in THF (12 mL) was added *n*-Bu_3SnH (1.6 mL, 6.0 mmol). After stirring at 25 °C for 2 h, the reaction mixture was diluted with hexane and filtered. Evaporation of the solvent and purification by chromatography (SiO_2, 93:5:2 hexane/AcOEt/Et_3N) afforded 1.10 g (60%) of **37** as a yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 1.07 (d, *J* = 6.4 Hz, 3H, C_6-CH_3), 1.11 (s, 3H, C_2-CH_3), 1.14 (t, *J* = 7.2 Hz, 9H, 3 x CH_3), 1.19 (t, *J* = 7.9 Hz, 6H, 3 x CH_2), 1.30 (s, 3H, C_2-CH_3), 1.4-1.9 (m, 18H, 9 x CH_2), 2.0-2.2 (m, 1H, H_6), 6.49 (d, *J* = 19.4 Hz, $^2J_{Sn\text{-}H}$ = 80.5/77.1 Hz, 1H, $H_{2'}$), 6.64 (d, *J* = 19.4 Hz, $^3J_{Sn\ H}$ = 71.3/68.2 Hz, 1H, $H_{1'}$) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 10.1 (t, $^1J_{Sn\text{-}C}$ = 339.7/324.8 Hz, 3x), 14.0 (q, 3x), 16.3 (q), 22.1 (t), 22.2 (q), 26.6 (q), 27.7 (t, $^2J_{Sn\text{-}C}$ = 52.4 Hz, 3x), 29.7 (t, 3x), 33.0 (t), 36.7 (q), 38.2 (s, C_2), 38.5 (d, C_6), 80.4 (s, C_1), 126.1 (d), 148.4 (d) ppm; IR (NaCl) ν 2957 (s, C-H), 2927 (s, C-H), 2870 (s, C-H), 2855 (s, C-H), 1463 (m), 1418 (w), 1376 (w), 1330 (w), 1292 (w), 1189 (w), 1074 (w), 999 (w), 958 (w), 689 (w) cm^{-1}; MS (FAB^+) 401 (M^+, 100), 400 (34), 399 (58), 398 (24), 397 (32), 291 (65), 289 (41), 287 (23), 281 (70), 221 (70), 297 (64), 179 (47), 176 (74), 175 (48); HRMS (FAB^+) calcd for $C_{19}H_{37}O^{120}Sn$ 401.1866, found 401.1863.

Ethyl 5,6-Dihydro-6-hydroxyretinoate (38). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (11 mg, 0.012 mmol), $AsPh_3$ (31 mg, 0.10 mmol), iodide **35** (0.15 g, 0.50 mmol), and stannane **37** (0.25 g, 0.55 mmol) in NMP (7 mL) was stirred at 60 °C for 16 h. Purification by chromatography (SiO_2, 90:10 hexane/EtOAc) afforded 93 mg (54%) of **38** as a yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 0.86 (d, *J* = 6.6 Hz, 3H, C_5-CH_3), 0.91 (s, 3H, C_1-CH_3), 1.0-1.2 (m, 7H, C_1-CH_3 + $CO_2CH_2C\underline{H}_3$ + H_4), 1.2-1.3 (m, 1H, H_4), 1.4-1.6 (m, 4H, $2H_2$ + $2H_3$), 1.7-1.9 (m, 1H, H_5), 1.79 (s, 3H, C_9-CH_3), 2.49 (s, 3H, C_{13}-CH_3), 4.12 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.98 (s, 1H, H_{14}), 6.07 (d, *J* = 15.7 Hz, 1H, H_8), 6.12 (d, *J* = 11.4 Hz, 1H, H_{10}), 6.19 (d, *J* = 15.1 Hz, 1H, H_{12}), 6.62 (d, *J* = 15.7 Hz, 1H, H_7), 6.92 (dd, *J* = 15.1, 11.4 Hz, 1H, H_{11}) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 13.6, 14.2, 14.8, 16.6, 22.4, 26.9, 33.3, 38.1, 38.8, 39.3, 60.0, 79.8, 120.0, 129.0, 131.1, 131.3, 135.2, 136.5, 138.6, 153.1, 167.3 ppm.

Ethyl Retinoate (11a). *p*-Toluenesulfonic acid monohydrate (24 mg, 0.13 mmol) was added, in one portion, to the solution of alcohol **38** (40 mg, 0.12 mmol) in benzene (2 mL). After stirring the mixture at 25 °C for 1.5 h, a saturated aqueous $NaHCO_3$ solution was added, and the mixture was extracted with Et_2O (3x). The combined organic extracts were washed with saturated $NaHCO_3$, water and brine, dried (Na_2SO_4) and evaporated. Purification of the residue by chromatography (SiO_2, 98:2 hexane/ethyl acetate) afforded 32 mg (85%) of ethyl retinoate **11a**.

Methyl (2*E*,4*E*)-3-Methyl-5-(tri-*n*-butylstannyl)penta-2,4-dienoate (17a). General Procedure for Aldehyde Oxidations. To a cooled (0 °C) solution of aldehyde **15a** (0.37 g, 0.96 mmol) in MeOH (5 mL) was added a mixture of KCN (0.31 g, 4.82 mmol) and MnO_2 (1.67 g, 19.26 mmol). After stirring at 0 °C for 2 h, the mixture was filtered, diluted with Et_2O, and washed with brine. The residue was purified by chromatography (SiO_2, 95:5 hexane/EtOAc) to afford 0.33 g (82%) of **17a** as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ 0.8-0.9 (m, 15H, 3 x CH_3 + 3 x CH_2), 1.2-1.3 (m, 6H, 3 x CH_2), 1.4-1.5 (m, 6H, 3 x CH_2), 2.25 (d, *J* = 1.1 Hz, 3H, C_3-CH_3), 3.71 (s, 3H, $CO_2C\underline{H}_3$), 5.74 (br s, 1H, H_2), 6.56 (d, *J* = 19.4 Hz, $^3J_{Sn\text{-}H}$ = 46.2 Hz, 1H, H_4), 6.80 (d, *J* = 19.4 Hz, $^2J_{Sn\text{-}H}$ = 51.3 Hz, 1H, H_5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0 (t, $^1J_{Sn\text{-}C}$ = 346.5/331.1 Hz, 3x), 13.5 (q), 14.0 (q, 3x), 27.6 (t, $^2J_{Sn\text{-}C}$ = 54.6 Hz, 3x), 29.4 (t, $^3J_{Sn\text{-}C}$ = 20.8 Hz, 3x), 51.4 (q, $CO_2C\underline{H}_3$), 118.6 (d), 138.4 (d, $^1J_{Sn\text{-}C}$ = 352.6/337.5 Hz, C_5), 149.4 (d, $^4J_{Sn\text{-}C}$ = 10.9 Hz, C_2), 153.3 (s,

$^3J_{Sn-C}$ = 62.5 Hz, C_3), 168.0 (s, C_1) ppm; IR (NaCl) ν 2955 (m, C-H), 2926 (m, C-H), 2852 (w, C-H), 1717 (s, C=O), 1615 (w, C=C), 1558 (w), 1435 (w), 1232 (m), 1152 (s) cm^{-1}; MS (EI$^+$) *m/z* (%) 359 ([M - Bu]$^+$, 75), 358 (28), 357 (56), 355 (32), 303 (81), 302 (28), 301 (60), 299 (35), 247 (100), 246 (32), 245 (77), 244 (28), 243 (46), 151 (62), 149 (46); HRMS (EI$^+$) calcd for $C_{19}H_{36}O_2{}^{120}Sn$ 416.1737, found 416.1726.

Methyl (2*E*,4*E*)-5-(Tri-*n*-butylstannyl)penta-2,4-dienoate (17b). Following the general procedure described above, a solution of aldehyde **15b** (0.35 g, 0.94 mmol) in MeOH (4.7 mL), was treated with a mixture of KCN (0.32 g, 4.93 mmol) and MnO_2 (1.63 g, 18.76 mmol) to afford, after purification by chromatography (SiO_2, 95:5 hexane/EtOAc), 0.37 g (98%) of **17b** as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.8-1.0 (m, 15H, 3 x CH_3 + 3 x CH_2), 1.2-1.4 (m, 6H, 3 x CH_2), 1.4-1.6 (m, 6H, 3 x CH_2), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 5.80 (d, *J* = 15.4 Hz, 1H, H_2), 6.64 (dd, *J* = 18.7, 9.9 Hz, $^3J_{Sn-H}$ = 54.3 Hz, 1H, H_4), 6.82 (d, *J* = 18.7 Hz, $^2J_{Sn-H}$ = 63.2 Hz, 1H, H_5), 7.19 (dd, *J* = 15.4, 9.9 Hz, $^4J_{Sn-H}$ = 5.2 Hz, 1H, H_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6 (t, $^1J_{Sn-C}$ = 347.8/335.1 Hz, 3x), 13.6 (q, 3x), 27.2 (t, $^2J_{Sn-C}$ = 54.4 Hz, 3x), 29.0 (t, $^3J_{Sn-C}$ = 20.4 Hz, 3x), 51.4 (q, $CO_2\underline{C}H_3$), 119.4 (d), 144.2 (d), 146.7 (d, $^2J_{Sn-C}$ = 69.9 Hz, C_4), 147.5 (d, $^1J_{Sn-C}$ = 340.8/327.2 Hz, C_5), 167.9 (s, C_1) ppm; IR (NaCl) ν 2956 (m, C-H), 2925 (m, C-H), 2853 (m, C-H), 1722 (s, C=O), 1626 (w, C=C), 1560 (w), 1458 (w), 1439 (w), 1273 (m), 1213 (m), 1154 (m), 1101 (w), 1010 (w) cm^{-1}; MS (EI$^+$) *m/z* (%) 345 ([M - Bu]$^+$, 100), 344 (36), 343 (73), 342 (28), 341 (41), 289 (53), 287 (40), 285 (23), 233 (76), 232 (24), 231 (61), 229 (36), 151 (41), 149 (32); HRMS (EI$^+$) calcd for $C_{18}H_{34}O_2{}^{120}Sn$ 402.1581, found 402.1581.

Pinacol [(1*E*,3*E*)-4-(2,6,6-Trimethylcyclohex-1-en-1-yl)buta-1,3-dienyl]borane (43). In accordance to the general procedure, boronate **43** was obtained as a yellow oil in 55% yield, starting from alkyne **40**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (s, 6H, $C_{6'}$-2CH_3), 1.28 (s, 12H, -OC(CH_3)$_2$C(CH_3)$_2$O-), 1.4-1.6 (m, 4H, $2H_{4'}$ + $2H_{5'}$), 1.71 (s, 3H, $C_{2'}$-CH_3), 2.00 (t, *J* = 5.7 Hz, 2H, $2H_{3'}$), 5.48 (d, *J* = 17.6 Hz, 1H, H_1), 6.13 (dd, *J* = 15.6, 10.3 Hz, 1H, H_3), 6.35 (d, *J* = 15.6 Hz, 1H, H_4), 7.07 (dd, *J* = 17.6, 10.3 Hz, 1H, H_2) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.1 (t), 21.6 (q), 24.7 (q, 4x, -OC($\underline{C}H_3$)$_2$C($\underline{C}H_3$)$_2$O-), 28.8 (q, 2x, $C_{6'}$-2$\underline{C}H_3$), 33.1 (t), 34.0 (s, $C_{6'}$), 39.6 (t), 83.1 (s, 2x, -O$\underline{C}$(CH_3)$_2$$\underline{C}$($CH_3$)$_2$O-), 131.1 (s), 135.0 (d, 2x), 136.1 (d), 137.2 (s), 151.1 (d) ppm; IR (NaCl) ν 2972 (m, C-H), 2930 (m, C-H), 2868 (m, C-H), 1603 (s), 1457 (s), 1361 (m), 1323 (m), 1256 (s), 1144 (s) cm^{-1}; MS (EI$^+$) *m/z* (%) 302 (M$^+$, 74), 287 (83), 286 (20), 231 (32), 217 (28), 187 (64), 175 (20), 131 (27), 129 (29), 119 (23), 101 (100), 93 (21), 84 (37); HRMS (EI$^+$) calcd for $C_{19}H_{31}BO_2$ 302.2417, found 302.2431.

2-[(1*E*,3*E*)-4-Iodobuta-1,3-dien-1-yl]-1,3,3-trimethylcyclohex-1-ene (41b). Following the general procedure described above, a cooled (-78 °C) solution of boronate **43** (0.15 g, 0.5 mmol) in THF (8 mL) was treated with a suspension of MeONa (54 mg, 1.0 mmol) in MeOH (2 mL) and with ICl (1.5 M in CH_2Cl_2, 0.34 mL, 0.5 mmol) to afford, after purification by chromatography (SiO_2, hexane), 0.13 g (87%) of **41b** as a yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 1.08 (s, 6H, C_3-2CH_3), 1.4-1.5 (m, 2H, $2H_5$), 1.5-1.6 (m, 2H, $2H_4$), 1.69 (s, 3H, C_1-CH_3), 1.9-2.0 (m, 2H, $2H_6$), 5.86 (dd, *J* = 15.7, 10.6 Hz, 1H, $H_{2'}$), 5.94 (d, *J* = 14.3 Hz, 1H, $H_{4'}$), 6.03 (d, *J* = 15.7 Hz, 1H, $H_{1'}$), 7.00 (dd, *J* = 14.3, 10.6 Hz, 1H, $H_{3'}$) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 19.5 (t), 21.9 (q), 28.8 (q, 2x), 33.3 (t), 34.2 (s), 39.8 (t), 77.4 (d, $C_{4'}$), 130.4 (s), 132.5 (d), 133.4 (d), 137.1 (s), 146.1 (d) ppm; IR (NaCl) ν 2957 (m, C-H), 2927 (s, C-H), 2864 (m, C-H), 1605 (w, C=C), 1457 (w), 1361 (w), 1310 (w), 979 (m) cm^{-1}; MS (EI$^+$) *m/z* (%) 302 (M$^+$, 8), 193 (9), 145 (9), 131 (8), 119 (13), 105 (37), 91 (14), 89 (100), 83 (19), 75 (98), 69 (21); HRMS (EI$^+$) calcd for $C_{13}H_{19}I$ 302.0532, found 302.0533.

(1*E*,3*E*)-2-Methyl-1-[(trifluoromethanesulfonyl)oxy]-4-(2,6,6-trimethylcyclohex-1-en-1-yl)buta-1,3-diene (46). A cooled (0 °C) solution of **44** (0.21 g, 1.0 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.37 g, 1.8 mmol) in CH_2Cl_2 (3.5 mL) was treated with trifluoromethanesulfonic anhydride (0.2 mL, 1.2 mmol). The mixture was stirred at 0 °C for 12 h and at 50 °C for an additional 1 h. After cooling down to 0 °C, hexane was added, the insoluble salts were removed by filtration and the solvent was evaporated. The residue was purified by chromatography (SiO_2, 95:5 hexane/EtOAc) to

afford 0.13 g (40%) of **46** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.01 (s, 6H, C_6-$2CH_3$), 1.3-1.5 (m, 4H, $2H_4$· + $2H_5$·), 1.56 (d, J = 1.2 Hz, 3H, C_2-CH_3), 1.61 (s, 3H, C_2-CH_3), 1.93 (t, J = 6.0 Hz, 2H, $2H_3$·), 5.60 (d, J = 16.1 Hz, 1H, H_3), 6.15 (d, J = 16.1 Hz, 1H, H_4), 6.44 (s, 1H, H_1) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6 (q), 19.4 (t), 21.5 (q), 28.8 (q, 2x), 30.3 (q), 32.9 (t), 34.2 (s), 39.6 (t), 116.6 (s), 128.7 (d), 130.1 (s), 130.8 (d), 134.9 (d), 137.3 (s) ppm; IR (NaCl) ν 2960 (m, C-H), 2930 (m, C-H), 2866 (m, C-H), 1615 (w), 1427 (s), 1387 (w), 1246 (s), 1212 (s), 1144 (s), 1042 (s), 1010 (m), 964 (w), 864 (m), 766 (w), 623 (m) cm^{-1}; MS (EI$^+$) *m/z* (%) 338 (M^+, 68), 279 (18), 205 (21), 177 (55), 149 (100), 121 (53), 119 (35), 107 (35), 105 (27), 95 (43), 91 (29); HRMS (EI$^+$) calcd for $C_{15}H_{21}F_3O_3S$ 338.1163, found 338.1162.

Methyl Retinoate (48a). Procedure A: Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (6.9 mg, 0.007 mmol), $AsPh_3$ (18.4 mg, 0.06 mmol), iodide **41a** (95 mg, 0.3 mmol), and stannane **17a** (137 mg, 0.33 mmol) in NMP (4 mL) was stirred at 60 °C for 3 h. Purification by chromatography (SiO_2, 95:5 hexane/EtOAc) afforded 60 mg (64%) of **48a** as a yellow oil. **Procedure B:** In accordance to the general procedure described above, the reaction of triflate **46** (50 mg, 0.15 mmol) and stannane **17a** (68 mg, 0.16 mmol) afforded, after purification by chromatography (SiO_2, 95:5 hexane/EtOAc), 46 mg (98%) of **48a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 6H, C_1-$2CH_3$), 1.4-1.6 (m, 4H, $2H_2$ + $2H_3$), 1.72 (s, 3H, C_5-CH_3), 2.01 (s, 3H, C_9-CH_3), 2.0-2.1 (m, 2H, $2H_4$), 2.36 (s, 3H, C_{13}-CH_3), 3.71 (s, 3H, $CO_2C\underline{H}_3$), 5.78 (s, 1H, H_{14}), 6.14 (d, J = 16.1 Hz, 1H, H_8), 6.14 (d, J = 11.5 Hz, 1H, H_{10}), 6.28 (d, J = 16.1 Hz, 1H, H_7), 6.29 (d, J = 15.0 Hz, 1H, H_{12}), 7.00 (dd, J = 15.0, 11.7 Hz, 1H, H_{11}) ppm.

Methyl 13-Desmethylretinoate (48b). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (6.9 mg, 0.007 mmol), $AsPh_3$ (18.4 mg, 0.06 mmol), iodide **41a** (95 mg, 0.3 mmol), and stannane **17b** (132 mg, 0.33 mmol) in NMP (4 mL) was stirred at 50 °C for 30 min. Purification by chromatography (SiO_2, 95:5 hexane/EtOAc) afforded 65 mg (73%) of **48b**[50] as a yellow solid (mp 95-100 °C, EtOH; lit.[50] 99-100.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 6H, C_1-$2CH_3$), 1.4-1.5 (m, 2H, $2H_3$), 1.5-1.6 (m, 2H, $2H_2$), 1.70 (s, 3H, C_5-CH_3), 1.98 (s, 3H, C_9-CH_3), 1.9-2.1 (m, 2H, $2H_4$), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 5.85 (d, J = 15.2, 1H, H_{14}), 6.13 (2d, J = 15.9 Hz, 2H, H_8 + H_{10}), 6.2-6.4 (m, 2H, H_7 + H_{12}), 6.94 (dd, J = 14.6, 11.8 Hz, 1H, H_{11}), 7.39 (dd, J = 15.1, 11.5 Hz, 1H, H_{13}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (q), 19.1 (t), 21.7 (q), 28.9 (q, 2x), 33.1 (t), 34.2 (s, C_1), 39.5 (t), 51.5 (q, $CO_2\underline{C}H_3$), 119.2 (d), 129.0 (d), 129.3 (d), 129.4 (d), 130.3 (s), 137.1 (d), 137.4 (d), 137.6 (s), 140.8 (s), 145.2 (d), 167.7 (s, C_{15}) ppm; IR (NaCl) ν 2928 (s, C-H), 2864 (m, C-H), 1717 (s, C=O), 1620 (m, C=C), 1583 (m), 1434 (m), 1319 (m), 1243 (s), 1172 (w), 1137 (s), 997 (m), 966 (w) cm^{-1}.

Methyl 9-Desmethylretinoate (48c). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (8.2 mg, 0.009 mmol), $AsPh_3$ (22 mg, 0.07 mmol), iodide **41b** (109 mg, 0.36 mmol), and stannane **17a** (166 mg, 0.40 mmol) in NMP (5 mL) was stirred at 50 °C for 5 h. Purification by chromatography (SiO_2, 95:5 hexane/EtOAc) afforded 72 mg (67%) of **48c**[50] as a yellow solid (mp 95-103 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 6H, C_1-$2CH_3$), 1.4-1.5 (m, 2H, $2H_3$), 1.5-1.6 (m, 2H, $2H_2$), 1.73 (s, 3H, C_5-CH_3), 2.0-2.1 (m, 2H, $2H_4$), 2.32 (s, 3H, C_{13}-CH_3), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 5.76 (s, 1H, H_{14}), 6.16 (dd, J = 15.6, 10.6 Hz, 1H, H_8), 6.2-6.3 (m, 3H, H_7 + H_{10} + H_{12}), 6.47 (dd, J = 14.6, 10.6 Hz, 1H, H_9), 6.68 (dd, J = 15.3, 10.7 Hz, 1H, H_{11}) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.6 (q), 19.1 (t), 21.7 (q), 28.9 (q, 2x), 33.3 (t), 34.1 (s, C_1), 39.7 (t), 50.9 (q, $CO_2\underline{C}H_3$), 118.2 (d), 130.4 (d), 131.3 (s), 132.9 (d), 134.2 (d), 134.7 (d), 135.2 (d), 137.5 (s), 137.6 (d), 152.8 (s), 167.6 (s, C_{15}) ppm; IR (NaCl) ν 3019 (w, C-H), 2929 (m, C-H), 2863 (m, C-H), 1712 (s, C=O), 1586 (m, C=C), 1439 (w), 1385 (w), 1357 (w), 1243 (m), 1154 (s), 997 (m) cm^{-1}; MS (EI$^+$) *m/z* (%) 300 (M^+, 100), 285 (26), 147 (15), 125 (17), 123 (15), 111 (15), 105 (18), 97 (24), 95 (17), 85 (27), 83 (25), 81 (19), 71 (34), 69 (37); HRMS (EI$^+$) calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2090.

Methyl 9,13-Bisdesmethylretinoate (48d). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (6.2 mg, 0.007 mmol), $AsPh_3$ (16.5 mg, 0.05 mmol), iodide **41b** (81 mg, 0.27 mmol), and stannane **17b** (120 mg, 0.3 mmol) in NMP (4 mL) was stirred at 50 °C for 30 min. Purification by chromatography (SiO_2, 95:5 hexane/EtOAc)

afforded 63 mg (81%) of **48d**[50] as a yellow solid (mp 103-107 °C, EtOH; lit.[50] 104-105 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 6H, C_1-2CH_3), 1.4-1.5 (m, 2H, $2H_3$), 1.5-1.6 (m, 2H, $2H_2$), 1.73 (s, 3H, C_5-CH_3), 2.0-2.1 (m, 2H, $2H_4$), 3.75 (s, 3H, CO_2CH_3), 5.86 (d, J = 15.2, 1H, H_{14}), 6.17 (dd, J = 15.6, 10.7 Hz, 1H, H_8), 6.2-6.3 (m, 3H, H_7 + H_{10} + H_{12}), 6.49 (dd, J = 14.7, 10.7 Hz, 1H, H_9), 6.62 (dd, J = 14.7, 11.2 Hz, 1H, H_{11}), 7.34 (dd, J = 15.2, 11.4 Hz, 1H, H_{13}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1 (t), 21.8 (q), 28.9 (q, 2x), 33.3 (t), 34.1 (s), 39.7 (t), 51.5 (q, $CO_2\underline{C}H_3$), 119.4 (d), 128.9 (d), 129.9 (d), 131.7 (s), 132.7 (d), 134.9 (d), 137.7 (s), 138.6 (d), 141.3 (d), 144.9 (d), 167.7 (s, C_{15}) ppm; IR (NaCl) ν 2921 (m, C-H), 2863 (w, C-H), 1710 (s, C=O), 1591 (m, C=C), 1435 (w), 1213 (m), 1155 (m), 1145 (m), 1011 (s) cm^{-1}; MS (EI$^+$) *m/z* (%) 286 (M^+, 63), 271 (47), 159 (20), 157 (21), 145 (21), 105 (23), 99 (22), 97 (32), 91 (35), 85 (74), 83 (36), 79 (20), 71 (100), 70 (22), 69 (51); HRMS (EI$^+$) calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1928.

Methyl 7,8-Dihydroretinoate (49a). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol), $AsPh_3$ (10 mg, 0.03 mmol), iodide **42** (50 mg, 0.16 mmol), and stannane **17a** (72 mg, 0.18 mmol) in NMP (3 mL) was stirred at 80 °C for 3 h. Purification by chromatography (SiO_2, 95:5 hexane/EtOAc) afforded 44 mg (87%) of **49a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 6H, C_1-2CH_3), 1.4-1.6 (m, 4H, $2H_2$ + $2H_3$), 1.62 (s, 3H, C_5-CH_3), 1.89 (d, J = 1.0 Hz, 3H, C_9-CH_3), 1.9-2.0 (m, 2H, $2H_4$), 2.1-2.2 (m, 4H, $2H_7$ + $2H_8$), 2.34 (s, 3H, C_{13}-CH_3), 3.71 (s, 3H, CO_2CH_3), 5.75 (s, 1H, H_{14}), 5.99 (d, J = 11.0 Hz, 1H, H_{10}), 6.20 (d, J = 15.1 Hz, 1H, H_{12}), 6.87 (dd, J = 15.1, 11.0 Hz, 1H, H_{11}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (q), 17.2 (q), 19.5 (t), 19.8 (q), 27.5 (t), 28.6 (q, 2x), 32.7 (t), 35.0 (s), 39.8 (t), 40.8 (t), 50.9 (q, $CO_2\underline{C}H_3$), 117.5 (d), 124.2 (d), 127.5 (s), 131.2 (d), 133.3 (d), 136.6 (s), 144.9 (s), 153.3 (s), 167.6 (s, C_{15}) ppm; IR (NaCl) ν 2923 (s, C-H), 2860 (m, C-H), 1722 (m, C=O), 1598 (m), 1451 (w), 1229 (w), 1036 (w) cm^{-1}; MS (EI$^+$) *m/z* (%) 316 (M^+, 11), 180 (50), 149 (23), 137 (100), 121 (24), 119 (19), 105 (18), 95 (55), 91 (23), 81 (37); HRMS (EI$^+$) calcd for $C_{21}H_{32}O_2$ 316.2402, found 316.2405.

Methyl 13-Desmethyl-7,8-dihydroretinoate (49b). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), $AsPh_3$ (12 mg, 0.04 mmol), iodide **42** (62 mg, 0.20 mmol), and stannane **17b** (87 mg, 0.22 mmol) in NMP (3 mL) was stirred at 80 °C for 1 h. Purification by chromatography (SiO_2, 95:5 hexane/AcOEt) afforded 47 mg (78%) of **49b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 6H, C_1-2CH_3), 1.4-1.6 (m, 2H, $2H_2$ + $2H_3$), 1.61 (s, 3H, C_5-CH_3), 1.88 (d, J = 0.6 Hz, 3H, C_9-CH_3), 1.92 (t, J = 6.1 Hz, 2H, $2H_4$), 2.0-2.2 (m, 4H, $2H_7$ + $2H_8$), 3.75 (s, 3H, CO_2CH_3), 5.84 (d, J = 15.2 Hz, 1H, H_{14}), 5.99 (d, J = 11.3 Hz, 1H, H_{10}), 6.25 (dd, J = 14.7, 11.4 Hz, 1H, H_{12}), 6.82 (dd, J = 14.7, 11.3 Hz, 1H, H_{11}), 7.38 (dd, J = 15.2, 11.4 Hz, 1H, H_{13}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1 (q), 19.4 (t), 19.7 (q), 27.3 (t), 28.5 (q, 2x), 32.7 (t), 34.9 (s), 39.7 (t), 40.7 (t), 51.3 (q, $CO_2\underline{C}H_3$), 118.8 (d), 124.0 (d), 127.5 (s), 127.6 (d), 136.5 (s), 137.6 (d), 145.5 (d), 146.4 (s), 167.7 (s, C_{15}) ppm; IR (NaCl) ν 2928 (s, C-H), 2865 (m, C-H), 1718 (s, C=O), 1613 (s), 1434 (m), 1382 (w), 1313 (m), 1258 (m), 1240 (m), 1157 (m), 1132 (s), 999 (m) cm^{-1}; MS (EI$^+$) *m/z* (%) 302 (M^+, 15), 166 (50), 138 (11), 137 (100), 107 (10), 105 (11), 95 (45), 81 (24); HRMS (EI$^+$) calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2256.

Methyl Retinoate (48a). Following the general procedure described above, a mixture of $Pd_2(dba)_3$ (5.7 mg, 0.006 mmol), $AsPh_3$ (15 mg, 0.05 mmol), iodide **24** (63 mg, 0.25 mmol), and stannane **47** (132 mg, 0.27 mmol) in NMP (2.5 mL) was stirred at 50 °C for 3 h. Purification by chromatography (SiO_2, 95:5 hexane/EtOAc) afforded 60 mg (76%) of **48a** as a yellow oil.

2-[(1*E*,3*E*,5*E*)-3-Methyl-6-(tri-*n*-butylstannyl)hexa-1,3,5-trien-1-yl]-1,3,3-trimethylcyclohex-1-ene (52). To a cooled (-30 °C) solution of phosphonium salt **50** (0.26 g, 0.55 mmol) in THF (3 mL) was added *n*-BuLi (2.6 M in hexane, 0.21 mL, 0.55 mmol). After stirring at 0 °C for 20 min, the mixture was cooled down to -30 °C and a solution of aldehyde **51**[53] (0.19 g, 0.5 mmol) in THF (2 mL) was slowly added. The reaction mixture was stirred at -30 °C for 1 h and at 25 °C for an additional 5 h. Et_2O was then added, the insoluble salts were removed by filtration, and the organic layer was washed

with saturated aqueous NH_4Cl and H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography (SiO_2 C-18, 5:95 CH_2Cl_2/CH_3CN) to afford 0.19 g (77%) of **52** as a yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 0.94 (t, J = 7.3 Hz, 9H, 3 x CH_3), 1.02 (t, J = 8.0 Hz, 6H, 3 x CH_2), 1.10 (s, 6H, C_3-$2CH_3$), 1.39 (sextet, J = 7.3 Hz, 6H, 3 x CH_2), 1.4-1.5 (m, 2H, $2H_4$), 1.5-1.7 (m, 8H, $2H_5$ + 3 x CH_2), 1.75 (s, C_1-CH_3), 1.93 (3H, d, J = 0.7 Hz, $C_{3'}$-CH_3), 1.9-2.0 (2H, m, $2H_6$), 6.25 (1H, d, J = 3H, 10.6 Hz, $H_{4'}$), 6.27 (s, 1H, $H_{1'}$ + $H_{2'}$), 6.47 (d, J = 18.4 Hz, $^2J_{Sn-H}$ = 73.2 Hz, 1H, $H_{6'}$), 7.21 (dd, J = 18.4, 10.6 Hz, $^2J_{Sn-H}$ = 61.0 Hz, 1H, $H_{5'}$) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 10.1 (t, $^1J_{Sn-C}$ = 327.2/342.5 Hz, 3x), 12.9 (q), 14.1 (q, 3x), 19.9 (t), 22.1 (q), 27.9 (t, $^2J_{Sn-C}$ = 53.6 Hz, 3x), 29.3 (q, 2x), 29.8 (t, $^3J_{Sn-C}$ = 20.7 Hz, 3x), 33.4 (t), 34.7 (s), 40.1 (t), 127.5 (d), 129.3 (s), 133.9 (d, $^2J_{Sn-C}$ = 72.8 Hz, C_2), 134.6 (d, $^1J_{Sn-C}$ = 393.3/375.9 Hz, $C_{6'}$), 134.7 (s), 138.4 (s), 138.8 (d), 144.1 (d) ppm; IR (NaCl) ν 2956 (s, C-H), 2926 (s, C-H), 2871 (m, C-H), 1716 (w), 1588 (s), 1463 (w), 1376 (m), 1077 (w), 878 (w), 674 (w) cm^{-1}; MS (FAB$^+$) m/z (%) 449 (36), 447 (29), 447 (17), 423 (17), 419 (100), 418 (43), 417 (78), 416 (33), 415 (43), 305 (17), 291 (37), 287 (18), 235 (28), 233 (24), 215 (19); HRMS (FAB$^+$) calcd for $C_{24}H_{41}{}^{120}Sn$ 449.2230, found 449.2227.

Ethyl (*E*)-3-Iodobut-2-enoate (57). Following the general procedure for tin/iodine exchange reactions described above, a solution of stannane **31** (0.21 g, 0.52 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of I_2 (0.14 g, 0.57 mmol) in CH_2Cl_2 (5 mL) to yield, after purification by chromatography (SiO_2, 95:5 hexane/EtOAc), 83 mg (67%) of **57** as a yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 0.87 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.76 (s, 3H, $3H_4$), 3.83 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 6.58 (d, J = 1.4 Hz, 1H, H_2) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 14.3 (q), 30.9 (q), 60.3 (t, $CO_2CH_2CH_3$), 120.6 (s, C_3), 132.1 (d, C_2), 163.9 (s, C_1) ppm; IR (NaCl) ν 2922 (s, C-H), 2852 (m, C-H), 1716 (m, C=O), 1617 (w), 1458 (m), 1375 (w), 1185 (w), 1074 (w), 758 (m) cm^{-1}.

Ethyl Retinoate (11a). In accordance to the general procedure for Stille reactions, iodide **57** (60 mg, 0.25 mmol) was coupled to stannane **52** (0.14 g, 0.27 mmol) after the reaction mixture was stirred at 25 °C for 4 h. Purification by chromatography (SiO_2, 98:2 hexane/EtOAc) afforded 80 mg (97%) of ethyl retinoate **11a** as a yellow oil.

(2*E*,4*E*)-5-Iodo-2-methylpenta-2,4-dien-1-ol (55). In accordance to the general procedure described above, a solution of dienylstannane **54** (0.20 g, 0.53 mmol) in CH_2Cl_2 (4 mL) was treated with a solution of I_2 (0.15 g, 0.58 mmol) in CH_2Cl_2 (5 mL) to afford, after purification by chromatography (SiO_2, 80:20 hexane/AcOEt), 0.09 g (79%) of dienyliodide **55**. ^1H NMR (250 MHz, $CDCl_3$) δ 1.67 (s, 3H, C_2-CH_3), 3.96 (s, 2H, $2H_1$), 5.96 (d, J = 10.9 Hz, 1H, H_3), 6.22 (d, J = 14.2 Hz, 1H, H_5), 7.21 (dd, J = 14.2, 10.9 Hz, 1H, H_4) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.2 (q, C_2-CH_3), 67.5 (t, C_1), 78.9 (d, C_5), 124.3 (s, C_2), 138.4 (d, C_4), 141.3 (d, C_3) ppm; UV (MeOH) λ_{max} 256 nm; MS (EI$^+$) m/z (%) 224 (M$^+$, 16), 207 (20), 127 (14), 111 (10), 97 (39), 95 (21), 80 (100), 77 (27), 69 (25); HRMS (EI$^+$) calcd for C_6H_9IO 223.9700, found 223.9709.

(2*E*,4*E*)-5-Iodo-2-methylpenta-2,4-dien-1-al (56). In accordance to the general procedure described above, a solution of dienyliodide **55** (0.09 g, 0.42 mmol) in CH_2Cl_2 (4 mL) was treated with MnO_2 (0.66 g, 7.58 mmol) to yield, after purification by chromatography (SiO_2, 95:5 hexane/AcOEt), 0.08 g (90%) of dienal **56**. ^1H NMR (250 MHz, $CDCl_3$) δ 1.73 (s, 3H, C_2-CH_3), 6.66 (d, J = 11.3 Hz, 1H, H_3), 7.01 (d, J = 14.3 Hz, 1H, H_5), 7.46 (dd, J = 14.3, 11.3 Hz, 1H, H_4), 9.38 (s, 1H, H_1) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (q, C_2-CH_3), 90.7 (d, C_5), 137.2 (s, C_2), 140.6 (d, C_4), 146.2 (d, C_3), 194.4 (d, C_1) ppm; IR (NaCl) ν 2916 (s, C-H), 2847 (m, C-H), 1672 (s, C=O), 1228 (m) cm^{-1}; UV (MeOH) λ_{max} 298 nm; MS (EI$^+$) m/z (%) 222 (M$^+$, 92), 127 (25), 95 (100), 67 (15), 66 (22), 65 (28); HRMS (EI$^+$) calcd for C_6H_7IO 221.9544, found 221.9538.

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