The Suzuki Coupling Reaction in the Stereocontrolled Synthesis of 9-*cis*-Retinoic Acid and Its Ring-Demethylated Analogues[†,1]

Yolanda Pazos, Beatriz Iglesias, and Angel R. de Lera*

Departamento de Química Orgánica, Facultade de Ciencias, Universidade de Vigo 36200 Vigo, Spain

qolera@uvigo.es

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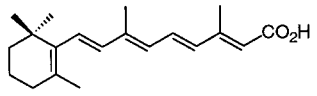
The thallium-accelerated Suzuki coupling reaction of tetraenyl iodide **19** and cyclohexenyl boronate **18** afforded ethyl 9-*cis*-retinoate (**12**) in high yield. Both coupling partners of the Suzuki reaction are better reacted immediately after generation from their precursors, tetraenylstannane **10** and cyclohexenyl iodide **13**. The geometrically homogeneous tetraenylstannane **10**, comprising the polyenic side chain of ethyl 9-*cis*-retinoate and its ring-demethylated analogues, was synthesized by a stereoselective Horner−Wadsworth−Emmons reaction. On the other hand, easily available cyclohexanones are ideal starting materials for preparation of the cyclohexenyl boronates required for the synthesis of the ring-modified 9-*cis*-retinoic acid analogues. For hindered cyclohexanones, hydrazones were converted to cyclohexenyl iodides. Iodine−lithium exchange and trapping with $B(OMe)_3$ then afforded the cyclohexenyl boronates. If the precursor cyclohexanone has secondary carbons, the alkenyllithium species was conveniently formed by elimination of the C,N-dilithiated intermediate obtained upon treating the trisylhydrazone with *n*-BuLi (Shapiro reaction). None of the above procedures allowed the generation of the more substituted organolithium from 2-methylcyclohexanone. However, the alternative Stille cross-coupling of **34** and **10** afforded 9-*cis*-1,1-bisdemethylretinoic acid **7**. Both Suzuki and Stille coupling reactions took place under mild conditions, and the preservation of the retinoid side-chain geometry was therefore secured.

Introduction

Retinoids, i.e., the natural and synthetic analogues of vitamin A,[2,3] act as modulators of nuclear transcription by binding to and activating two subfamilies of nuclear receptors,[4] namely the RXRs,[5] which use 9-*cis*-retinoic acid (**2**, Figure 1) as native ligand, and the RARs,[6] activated by both 9-*cis*-retinoic acid (**2**) and *trans*-retinoic acid (**1**). Genetic studies in mouse confirmed earlier in vitro findings, indicating that the functional unit transducing the retinoid signal was in fact a dimeric association of both nuclear receptors (RXR−RAR heterodimers).[4] It was then postulated that, upon activation by binding the retinoid ligands and subsequent conformational change, the heterodimers activate other components of the transcription machinery, a step also coupled to the dissociation from corepressors. This sequence of events results in the regulation of important gene networks which control fundamental processes of cell differentiation, homeostasis, morphogenesis, growth, development, and immune function.[2]



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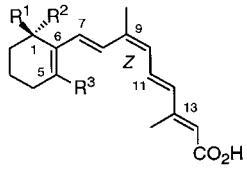

2, $R^1 = R^2 = R^3 = CH_3$
3, $R^1 = R^2 = R^3 = H$
4, $R^1 = R^3 = H$, $R^2 = CH_3$
5, $R^1 = R^2 = CH_3$, $R^3 = H$
6, $R^1 = R^3 = CH_3$, $R^2 = H$
7, $R^1 = R^2 = H$, $R^3 = CH_3$

Figure 1. Retinoid receptor native ligands (**1**, **2**) and analogues of 9-*cis*-retinoic acid modified on the cyclohexenyl ring.

* Corresponding author. Phone: + (34) 986 812316. Fax: + (34) 986 812382.

† Abbreviations: PPAR, peroxisome proliferator-activated receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; TR, thyroid receptor; VDR, vitamin D_3 receptor.

(1) Part of this work has already been published in preliminary form: Pazos, Y.; de Lera, A. R. *Tetrahedron Lett.* **1999**, *40*, 8287−8290.

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The described mechanism of gene regulation through the formation of RAR−RXR heterodimers is shared by other members of the nuclear receptor superfamily (VDR, PPAR, TR) which also heterodimerize with RXR.[4] The finding that RXR is the receptor playing the central role in gene regulation by lipophilic hormones (retinoids, eicosanoids, vitamin D_3, etc.) makes the design and clinical evaluation of RXR agonists and antagonists an active area of research. The first objective is now at reach since the crystal structure of the human RXRα ligand binding domain bound to its cognate ligand 9-*cis*-retinoic acid has recently been disclosed.[7] In this regard, some synthetic retinoid structures barely resembling that of the cognate ligand have shown RXR agonist[8] and antagonist activity.[9] It is rather surprising that no studies have been carried out on the biological activity of close structural analogues of the native ligand. We therefore set out to study the binding affinities of analogues with minor modifications (methyl group deletions) in the hydrophobic region of 9-*cis*-retinoic acid (**2**), while keeping the polyene skeleton C7−C15 intact (demethylated analogues **3**−**7**). It was expected that those structural alterations, transmitted to the protein through conformational and hydrophobic interactions, would result in biological profiles that might help to understand the "natural selection" of the RXR ligand. Since only the 9-cis isomers were of interest in this study, we planned to stereoselectively build the polyene skeketon by direct C6−C7 single-bond construction. For this purpose, we turned our attention to palladium-catalyzed cross-coupling reactions,[10] a process which we have found highly reliable to access fully conjugated polyenes.[11] This approach to Csp^2-Csp^2 bond construction has indeed been successfully implemented for the synthesis of the native RXR ligand, 9-*cis*-retinoic acid (**2**),[1] using a Suzuki cross-coupling reaction[12] that attaches the intact C7−C15 polyene side-chain (retinoid numbering) to the cyclohexenyl fragment. The cyclohexenyl boronic acid was in turn synthesized by trapping the alkenyllithium reagent resulting from iodine−lithium exchange with a trialkylborate (see Scheme 3). We subsequently found that the less-hindered analogues could be most conveniently obtained through a combined Shapiro[13]−Suzuki process, starting from the corresponding trisylhydrazones. We report here a full account of this approach to **2** and its ring-demethylated analogues **3**−**6**, as well as the preparation of retinoid **7** using the alternative Stille cross-coupling.[14]

Results and Discussion

At the outset, and based on our recently reported procedure for direct retinoid synthesis using the Stille reaction between tetraalkenyl stannanes and cyclohexenyl triflates,[11g,h] which successfully provided ethyl *trans*-retinoate (**8** + **9** → **11**) and the entire series of derivatives modified at the hydrophobic ring (the ethyl esters of the trans isomers of compounds **3**−**7**), we considered coupling of stannane **10** and cyclohexenyl triflate **8** to be the most direct approach to the desired ring-modified analogues with 9-cis geometry (Scheme 1).

Tetraenyl stannane **10** was obtained in high yield from the condensation of aldehyde **15** (prepared by oxidation of known stannyl dienol **14**[15]) and the carbanion derived from diethyl 3-(ethoxycarbonyl)-3-methylprop-2-enylphosphonate in the presence of DMPU[16a] (Scheme 2). Extensive experimentation revealed that the *E*/*Z* ratio of the newly formed double bond was critically dependent upon the temperature at which the condensation was performed. Therefore, temperatures of −115 °C were required to provide in a highly stereoselective manner tetraenyl stannane **10** in 94% yield.

As a drawback of the $C_9 + C_{11}$ Stille approach to retinoids (**8** + **9**, Scheme 1), we found that coupling temperatures increased with the steric hindrance of the cyclic electrophile.[11g] Under optimal experimental conditions [Farina's $Pd_2(dba)_3$, $AsPh_3$, NMP, 40 °C],[17] mixtures of product **12** and the trans isomer **11** were invariably obtained in the reaction of triflate **8** and stannane **10** (Scheme 1). The more reactive[10] cyclohexenyl iodide **13** coupled with tetraenyl stannane **10** at a lower reaction temperature (25 °C), but conversions were unacceptably slow (ca. 25% conversion after 24 h).

Previous studies have shown that the Suzuki reaction is more tolerant than the Stille coupling to the steric hindrance of the coupling partners.[18] The use of alkenyl boronic acids has been previously explored in our retinoid program for the formation of the C10−C11 bond.[11b] In our experience, the main limitation of this approach to

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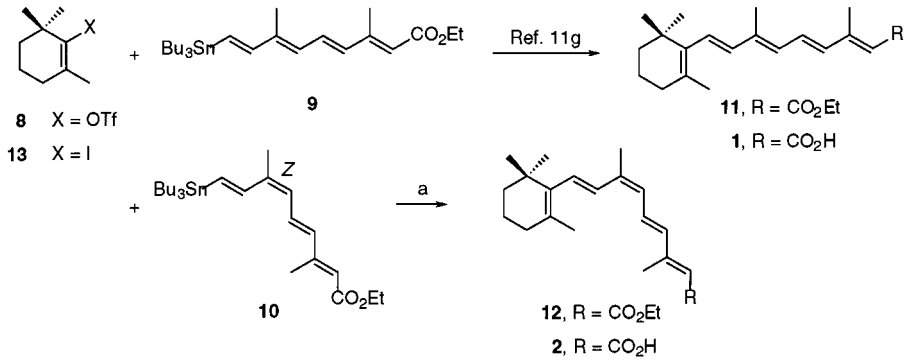
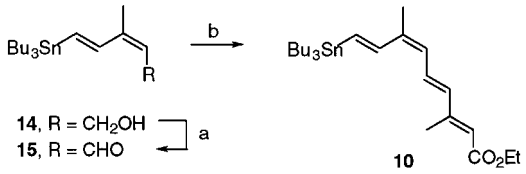
Scheme 1[a]



[a] (a) $Pd_2(dba)_3$, $AsPh_3$, NMP, 40 °C.

Scheme 2[a]



[a] (a) MnO_2, K_2CO_3, CH_2Cl_2, 0 to 25 °C, 2 h, 92%. (b) diethyl 3-(ethoxycarbonyl)-3-methylprop-2-enylphosphonate, *n*-BuLi, DMPU, THF, −115 to −40 °C, 94%.

retinoids[11a−c] and other sensitive polyenes[11e,f] is the difficult handling and tedious purification of the boronic acid (or ester) intermediates. Keay et al.[19a] overcome this drawback using the boronic acid immediately after its generation by trapping the alkenyllithium precursor with $B(OMe)_3$. Moreover, since alkenyllithium derivatives can be conveniently prepared by Shapiro reaction starting from the corresponding hydrazones, both reactions (Shapiro−Suzuki) were combined to induce coupling of Csp^2 fragments without isolation of the intermediates.[19b] This variant for boronic acid formation was particularly appealing because the precursor hydrazone could itself be derived from the cyclohexanone, the same starting material employed in the preparation of the cyclohexenyl triflates required for the synthesis of the trans retinoids by Stille reaction (Scheme 1).[11g,h] Unfortunately, we faced the lack of reactivity of the common hydrazones derived from 2,6,6-trimethylcyclohexanone **16** (trisyl, tosyl, and even the unsubstituted hydrazone **17**, Scheme 3) under Shapiro's conditions. Since hydrazones are also precursors of alkenyl iodides,[20] cycloalkenyllithium derivatives could alternatively result from iodine−lithium exchange. In the event, cyclohexenyl iodide **13** was obtained by a modification of Barton's method[20a] using a solution of I_2 in ether in the presence of DBN.[20b] Iodine−lithium exchange using *t*-BuLi in THF at −78 °C for 30 min, followed by trapping the organolithium with $B(OMe)_3$,[19a] provided the putative boronic ester **18** (Scheme 3).

The second component, tetraenyl iodide **19**, had to be acquired immediately prior to use, by titration of **10** with a solution of iodine in dichloromethane[21] (Scheme 3), due to the proven instability of polyenyl iodides. The solvent was then removed and replaced by THF, and this solution was immediately added dropwise to a THF solution of $Pd(PPh_3)_4$ and the organoborane **18**, freshly prepared from **13**. After stirring for 10 min at room temperature, 10% aqueous TlOH[22] was added, and stirring was continued for 3 h. Workup and purification provided ethyl 9-*cis*-retinoate **12** in a satisfactory 84% combined yield from starting components **13** and **10**.[23] Last, basic hydrolysis of **12** yielded the desired 9-*cis*-retinoic acid (**2**)[16] (Scheme 3).

This new synthetic approach to 9-*cis*-retinoic acid (**2**) based on the Suzuki coupling to construct the C6−C7 bond does not require the isolation of organoboranes and other unstable intermediates and proceeds under mild reaction conditions compatible with the lability of the cis isomers. Since cyclohexenyl boronic ester **18** is ultimately derived from cyclohexanone **16**, the synthetic scheme should be easily adapted to the preparation of the ring-demethylated analogues.

Despite the failure to induce a Shapiro reaction starting from the highly hindered ketone **16**, we felt that the demethylated cyclohexanones should more easily be converted into the alkenyllithium derivatives through Shapiro reaction of the corresponding arenesulfonylhydrazones.[24] For the implementation of the Shapiro−Suzuki sequence, trisylhydrazones were selected due to reports of fast decomposition (approximately 2 min at 0 °C) of the dianion formed upon treatment with *n*-BuLi, a reaction that can be performed in THF.[13b] Trisylhydrazones are usually prepared by mixing equimolecular amounts of both reactants, the ketone and trisylhydrazine, dissolved in methanol, ethanol,[25a] or diethyl ether[25b] (in the presence of an acid catalyst such as hydrochloric acid) allowing the reaction to proceed at 25 °C. The trisylhydrazone is isolated in good yield by filtration of the precipitate obtained upon cooling the reaction mix-

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(23) An alternative, less efficient synthesis of 9-*cis*-retinoic acid (**2**), based on a Suzuki cross-coupling of the in situ generated alkenyl boronic ester **18** and a shorter polyenic component (a dienyl iodide), has been previously published by our group (see ref 1). This sequence, although stereoselective, faced the limitation of the low yields obtained in both the Suzuki coupling and the HWE steps, requiring moreover the difficult handling of sensitive trienol and dienol intermediates.

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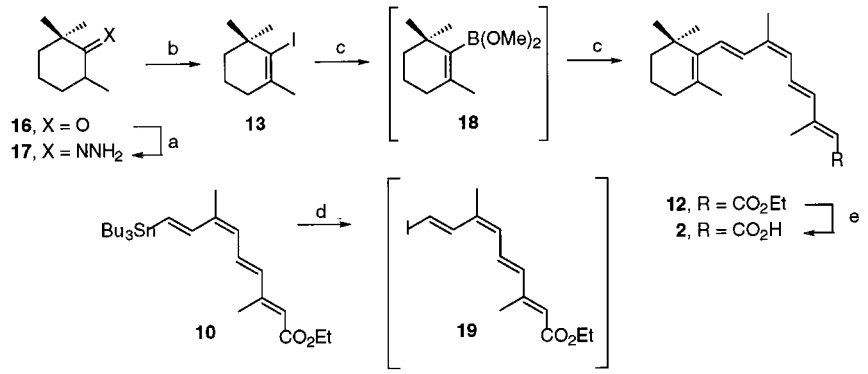
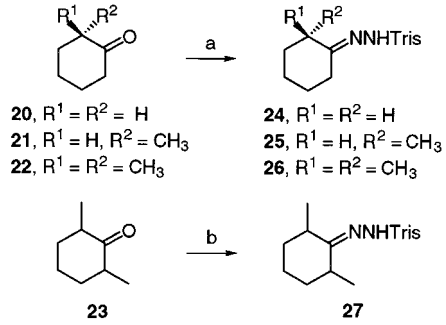
Scheme 3[a]



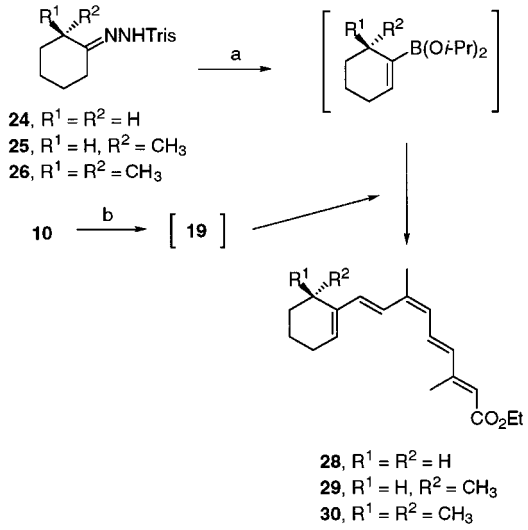
[a] (a) $H_2NNH_2 \cdot H_2O$, Et_3N, EtOH, 80−90%. (b) I_2, DBN, ether, 70−75%. (c) i. *t*-BuLi, THF, −78 °C; ii. $B(OMe)_3$, −78 to 0 °C; iii. $Pd(PPh_3)_4$, **19**, 10% aq TlOH, 25 °C, 3 h, 84%. (d) I_2, CH_2Cl_2, 25 °C. (e) 5 M KOH, EtOH, 70 °C, 91%.

Scheme 4[a]



[a] (a) $TrisNHNH_2$, MeOH, cat. concentrated HCl (**24**, ref 27a; **25**, refs 27a, 28; **26**, 75%). (b) $TrisNHNH_2$, CH_3CN, concentrated HCl, ref 29.

Scheme 5[a]



[a] (a) i. *n*-BuLi, −78 → 0 °C; ii. $B(Oi\text{-}Pr)_3$, −78 → 0 °C; iii. iodide **19**, $Pd(PPh_3)_4$, 10% aq TlOH, 25 °C (**28**, 0.5 h, 65%; **29**, 1 h, 91%; **30**, 1 h, 97%). (b) I_2, CH_2Cl_2, 25 °C.

ture. Although trisylhydrazine is an expensive reagent, it can be prepared from the corresponding sulfonyl chloride and hydrazine hydrate.[26]

Trisylhydrazones **24**,[27a] **25**,[27a,28] and **26**, were subjected to the Shapiro−Suzuki sequence for generation of the cyclohexenyl boronates and their coupling with tetraenyl iodide **19** (Scheme 5). After treating the trisylhydrazones with *n*-BuLi in THF at −78 °C and warming up to 0 °C to induce the elimination from the dianion (N_2 evolution was observed), subsequent treatment of the resultant cyclohexenyllithium with $B(Oi\text{-}Pr)_3$ at −78 °C and then at 0 °C, afforded the corresponding boronic esters. Sequential addition of $Pd(PPh_3)_4$, a solution of tetraenyl iodide **19** in THF, and a 10% aqueous TlOH solution afforded, after stirring at 25 °C, workup, and purification, the desired ethyl retinoate analogues (**28**−**30**) in good yields (Scheme 5). In keeping with the strong preference for deprotonation at the least substituted α-position (RCH_3 > R_2CH_2 > R_3CH) exhibited by the Shapiro reaction,[27] trisylhydrazone **25** afforded regioselectively retinoid **29**.

The inefficient generation of a cyclohexenyl boronate from hydrazone **27** (Scheme 4) confirms that steric hindrance in hydrazones with tertiary carbons at Cα slows down hydrogen abstraction (even using strong bases such as *s*-BuLi in TMEDA),[29] and addition to the imine carbon competes with elimination.[30] Therefore, synthesis of ethyl 9-*cis*-1-demethylretinoate **33** required instead the iodine−lithium exchange variant, as described in Scheme 3, to access the cyclohexenyl boronate. Thus, treatment of hydrazone **31** (mixture of diastereoisomers) with iodine and DBN provided alkenyl iodide **32**, which was treated with *t*-BuLi in THF at −78 °C, followed by addition of $B(OMe)_3$, to afford the nonisolated boronate. The application of the general procedure for the Suzuki coupling described above provided ethyl 9-*cis*-1-demethylretinoate **33** in excellent yield (93%) (Scheme 6).

A second limitation of the Shapiro reaction for trisylhydrazones with different substitution pattern is the inability to generate the more substituted cycloalkenyllithium intermediate by nitrogen elimination from the dianion.[13] Therefore, for the synthesis of ethyl 9-*cis*-1,1-

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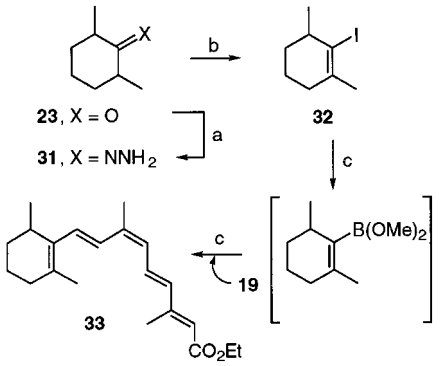
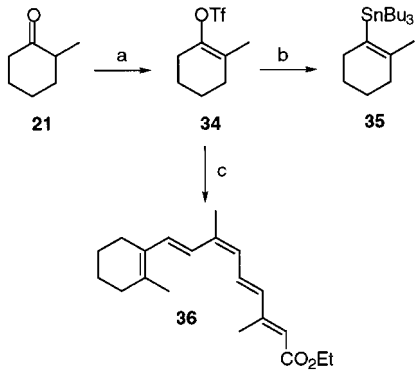
Scheme 6[a]



[a] (a) $H_2NNH_2 \cdot H_2O$, Et_3N, EtOH, 85%. (b) I_2, DBN, Et_2O, 65%. (c) i. *t*-BuLi, THF, −78 °C; ii. $B(OMe)_3$, −78 → 0 °C; iii. $Pd(PPh_3)_4$, iodide **19**, 10% aq TlOH, 25 °C, 3 h, 93%.

Scheme 7[a]



[a] (a) i. *i*-Pr_2NH, MeMgBr, 0 °C; ii. *N*-phenyltriflimide, THF, 0 °C (refs 11 g, 34, 35; 63%). (b) i. $(Bu_3Sn)_2Cu(CN)Li_2$, −50 → −20 °C, 2 h. ii. AgOAc, 25 °C, 2 h (refs 34b, 36; 91%). (c) Stannane **10**, $Pd_2(dba)_3$, $AsPh_3$, NMP, 25 °C, 3 h, 95%.

bisdemethylretinoate **36** recourse was also made to the iodine−lithium variant (Scheme 7). The regioselective formation of the thermodynamic magnesium enolate derived from 2-methylcyclohexanone has been previously described using diisopropylamidylmagnesium bromide.[31] Triflate **34**,[11g,31,32] obtained by trapping the enolate with *N*-phenyltriflimide, was converted into alkenyl stannane **35**,[32b,33] by treatment with a stannyl cuprate prepared from CuCN and Bu_3SnLi. Unfortunately, all attempts to effect the tin−lithium exchange met with failure. On the other hand, conversion of stannane **35** into the corresponding cycloalkenyl iodide[34] afforded mixtures of difficult separation. Likewise, transformation of this stannane into the corresponding vinyl bromide,[32b] by treatment with a solution of Br_2 in CH_2Cl_2, led to the desired compound, admixed with starting material and addition products, which were difficult to separate by column chromatography (SiO_2, C_{18}-SiO_2). Last, since triflate **34** is not sterically hindered, a Stille coupling[14] was alternatively contemplated (Scheme 7).[11g,h] Using Farina's optimized conditions [$Pd_2(dba)_3$ (2.5 mol %), $AsPh_3$ (20 mol %) in NMP],[17] alkenyl triflate **34** was coupled to tetraenyl stannane **10** at 25 °C in 3 h,[11h] to obtain the desired ethyl 9-*cis*-1,1-bisdemethylretinoate **36** in excellent yield (95%).

To complete the preparation of the desired 9-*cis*-retinoic acid analogues, ethyl 9-*cis*-retinoates (**28**−**30**, **33**, and **36**) were saponified (5 M KOH) at 70 °C for 30 min,[16a] affording the carboxylic acids (**3**−**7**) in high yields (85−95%). Their biological activities, including binding to RXRα, will be described elsewhere.

In summary, a new straightforward approach to 9-*cis*-retinoic acid (**2**) and its ring-demethylated analogues **3**−**7** has been developed, which builds the C6−C7 bond of the polyene skeleton by the C_9 (down to C_6, for the demethylated retinoids) + C_{11} strategy using as key step a Suzuki reaction without isolation of the unstable boronic acids and tetraenyl iodide **19**. For some of those ring-modified analogues a combined Shapiro−Suzuki reaction represents the shortest route. Alternative procedures (Suzuki reaction with an organoborane generated in situ by iodine−lithium exchange or Stille reaction) have been used as well, affording the polyenes in high yield and configurational fidelity.

Experimental Section

General Procedures.[11g,h] (Abbreviations: DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; NMP, 1-methyl-2-pyrrolidinone).

(2*Z*,4*E*)-3-Methyl-5-(tri-*n*-butylstannyl)penta-2,4-dienal (15). MnO_2 (8.31 g, 0.10 mol) and K_2CO_3 (13.2 g, 0.10 mol) were added to a stirred solution of alcohol **14**[15b] (2.06 g, 5.32 mmol) in CH_2Cl_2 (38 mL). After stirring for 30 min at 25 °C, the suspension was filtered through Celite, and the filtrate was evaporated. Purification of the residue by column chromatography (SiO_2, 90:8:2 hexane/EtOAc/Et_3N) afforded 1.88 g (92%) of **15** as a yellow oil. FTIR (NaCl) ν 1673 (s) cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 0.9−1.1 (m, 15H), 1.3−1.4 (m, 6H), 1.5−1.6 (m, 6H), 1.64 (s, 3H), 5.84 (d, J = 7.5 Hz, 1H), 6.78 (dt, J = 19.2 Hz, $^2J_{Sn-H}$ = 64.3 Hz, 1H), 7.69 (dt, J = 19.2 Hz, $^3J_{Sn-H}$ = 60.1 Hz, 1H), 10.37 (d, J = 7.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, C_6D_6) δ 10.0, 14.1, 20.5, 27.8, 29.7, 128.4, 141.3, 141.9, 153.5, 189.0 ppm. HRMS (EI^+) calcd for $C_{18}H_{34}O^{120}Sn$ 386.1632, found 386.1639.

Ethyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(tri-*n*-butylstannyl)-nona-2,4,6,8-tetraenoate (10). A cold (0 °C) solution of diethyl 3-(ethoxycarbonyl)-3-methylprop-2-enylphosphonate (1.80 g, 6.80 mmol) in THF (15.0 mL) was treated with DMPU (1.62 mL, 13.38 mmol) and *n*-BuLi (2.8 mL, 2.35 M in hexanes, 6.57 mmol). After stirring the mixture at 0 °C for 20 min, it was cooled to −115 °C and a solution of aldehyde **15** (1.74 g, 4.53 mmol) in THF (15.0 mL) was slowly added. The reaction mixture was stirred at −115 °C for 30 min, and then it was allowed to warm to −40 °C to complete the reaction. A saturated aqueous NH_4Cl solution was added, and the reaction mixture was extracted with Et_2O (3×). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by column chromatography (SiO_2−C_{18}, 60:40 CH_3CN/MeOH) afforded 2.10 g of **10** (94%) as a yellow oil. FTIR (NaCl) ν 1711 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H), 0.9−1.1 (m, 15H), 1.2−1.4 (m, 6H), 1.5−1.7 (m, 6H), 1.94 (s, 3H), 2.34 (d, J = 0.7 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H), 5.77 (s, 1H), 6.09 (d, J = 11.4 Hz, 1H), 6.22 (d, J = 15.1 Hz, 1H), 6.47 (dt, J = 19.1 Hz, $^2J_{Sn-H}$ = 68.9 Hz, 1H), 7.16 (dd, J = 15.1, 11.4 Hz, 1H), 7.19 (dt, J = 19.1 Hz, $^3J_{Sn-H}$ = 63.0 Hz, 1H) ppm. ^{13}C NMR (100

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MHz, $CDCl_3$) δ 9.7, 13.6, 13.7, 14.3, 20.3, 27.3, 29.1, 59.6, 118.9, 128.0, 129.4, 133.6, 134.9, 138.8, 142.1, 152.5, 167.1 ppm. HRMS (EI^+) calcd for $C_{25}H_{44}O_2{}^{118}Sn$ 494.2357, found 494.2361.

2,2,6-Trimethylcyclohexanone Hydrazone (17). General Procedure for the Preparation of Hydrazones. A solution of ketone **16** (0.50 g, 3.57 mmol) in absolute EtOH (2.5 mL) was treated with $H_2NNH_2{\cdot}H_2O$ (3.1 mL, 0.06 mol) and Et_3N (0.75 mL, 5.39 mmol). The reaction mixture was stirred at 100 °C until TLC monitoring showed complete disappearance of the starting material (approx 2−3 days). After evaporation of the solvent and the excess of reagents, the crude was extracted with Et_2O (3×). The combined organic layers were dried (Na_2SO_4) and evaporated. Purification of the residue by column chromatography (neutral alumina, grade II, 75:25 hexane/EtOAc) afforded a white solid (mp 67 °C), identified as **17** (0.48 g, 87%). FTIR (NaCl) ν 3600−3100 (br), 1637 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.13 (s, 3H), 1.16 (d, J = 7.5 Hz, 3H), 1.3−1.9 (m, 6H), 2.8−3.0 (m, 1H), 4.6−5.1 (br s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 17.4, 26.5, 28.9, 29.5, 31.7, 37.6, 40.4, 162.5 ppm. HRMS (EI^+) calcd for $C_9H_{18}N_2$ 154.1470, found 154.1477.

1,3,3-Trimethyl-2-iodocyclohex-1-ene (13). General Procedure for the Preparation of Alkenyl Iodides. To a solution of hydrazone **17** (0.40 g, 2.59 mmol) and excess DBN (2.88 mL, 23.34 mmol) in Et_2O (10 mL) was added dropwise a solution of iodine (1.36 g, 5.37 mmol) in Et_2O (10 mL). The mixture became turbid, and by the end of the addition a brown layer had formed. After 15 min of additional stirring, a saturated aqueous $NaHCO_3$ solution was added. The organic phase was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The resultant dark red oil was dissolved in benzene (10 mL), and the solution was then refluxed in the presence of DBN for 2.5 h. After cooling to room temperature, the mixture was poured into Et_2O and washed with a 1 M aqueous $Na_2S_2O_3$ solution (3×). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography (SiO_2, hexane) to afford 0.47 g of iodide **13** (73%) as a pale yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 1.20 (s, 6H), 1.3−1.6 (m, 4H), 1.88 (s, 3H), 1.7−1.9 (m, 2H) ppm. ^{13}C NMR (100 MHz, C_6D_6) δ 19.7, 31.2, 31.7 (25), 33.7, 38.0, 39.7, 117.6, 137.7 ppm. HRMS (EI^+) calcd for $C_9H_{15}I$ 250.0219, found 250.0210.

Ethyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate (12).[16a−b] **General Procedure for the Suzuki Reaction.** A cold (−78 °C) solution of iodide **13** (0.09 g, 0.38 mmol) in THF (2 mL) was treated with *t*-BuLi (0.47 mL, 1.70 M in pentane, 0.80 mmol). After stirring for 1 h, $B(OMe)_3$ (0.08 mL, 0.75 mmol) was added, and the reaction mixture was stirred at 0 °C for an additional 1 h. $Pd(PPh_3)_4$ (0.035 g, 0.030 mmol) was added, followed by iodide **19** [simultaneously generated by treatment of stannane **10** (0.15 g, 0.30 mmol) with a solution of iodine in CH_2Cl_2] in THF (0.6 mL), and a 10% aqueous TlOH solution (2.6 mL, 1.16 mmol). After stirring for 3 h at 25 °C, the reaction mixture was diluted with Et_2O and filtered through Celite. The organic layer thus obtained was washed with a saturated aqueous $NaHCO_3$ solution (3×), dried (Na_2SO_4), and evaporated. Purification of the residue by column chromatography (SiO_2, hexane/EtOAc), afforded 0.08 g of **12** (84%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.4−1.7 (m, 4H), 1.76 (s, 3H), 2.00 (s, 3H), 1.9−2.0 (m, 2H), 2.34 (d, J = 1.0 Hz, 3H), 4.17 (q, J = 7.1 Hz, 2H), 5.77 (s, 1H), 6.06 (d, J = 11.5 Hz, 1H), 6.22 (d, J = 15.1 Hz, 1H), 6.28 (d, J = 16.0 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 7.09 (dd, J = 15.1, 11.5 Hz, 1H) ppm.

Ethyl (2*E*,4*E*,6*Z*,8*E*)-(Cyclohex-1-en-1-yl)-3,7-dimethylnona-2,4,6,8-tetraenoate (28). General Procedure for the One-Pot Shapiro−Suzuki Reaction. A solution of *n*-BuLi in hexane (0.37 mL, 3.07 M, 1.14 mmol) was added to a cold (−78 °C) suspension of **24**[27a] (0.14 g, 0.38 mmol) in THF (1.0 mL), and the solution was stirred for 30 min. Nitrogen evolution was observed when the temperature was taken up to 0 °C, before cooling to −78 °C for the addition of triisopropyl borate (0.17 mL, 0.75 mmol). The mixture was stirred for 1 h at 0 °C and then heated to room temperature. $Pd(PPh_3)_4$ (0.035 g, 0.030 mmol), followed by iodide **19** [simultaneously generated by treating stannane **10** (0.15 g, 0.30 mmol) with a solution of iodine in CH_2Cl_2] dissolved in THF (1.0 mL), were then added. After stirring for 10 min, a 10% solution of TlOH in water was added (2.6 mL, 1.16 mmol), and the final mixture was stirred at 25 °C for 30 min. It was then diluted with Et_2O and filtered through Celite. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution (3×), dried (Na_2SO_4), and evaporated. The crude residue was purified by column chromatography (SiO_2, 90:10 hexane/EtOAc) to afford **28** (0.06 g, 65%) as a yellow solid (mp 77.5 °C, hexane/EtOAc). FTIR (NaCl) ν 1710 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 1.6−1.8 (m, 4H), 1.98 (s, 3H), 2.0−2.3 (m, 4H), 2.36 (s, 3H), 4.17 (q, J = 7.1 Hz, 2H), 5.77 (s, 1H), 5.90 (br s, 1H), 6.05 (d, J = 11.5 Hz, 1H), 6.21 (d, J = 15.1 Hz, 1H), 6.37 (d, J = 15.8 Hz, 1H), 6.73 (d, J = 15.8 Hz, 1H), 7.21 (dd, J = 15.1, 11.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.3, 21.0, 22.4, 22.5, 24.6, 26.3, 59.6, 118.5, 121.1, 128.4, 129.6, 132.2, 134.5, 134.8, 136.1, 138.2, 152.7, 167.2 ppm. HRMS (EI^+) calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1935.

(2*E*,4*E*,6*Z*,8*E*)-9-(Cyclohex-1-en-1-yl)-3,7-dimethylnona-2,4,6,8-tetraenoic Acid (3). General Procedure for the Hydrolysis of Esters. A solution of ester **28** (0.03 g, 0.10 mmol) in EtOH (0.2 mL) was treated with a 5 M aqueous KOH solution (0.19 mL) and then refluxed for 30 min. The solution was cooled to 25 °C, acidified with 10% HCl, and then extracted with a 70:30 Et_2O/CH_2Cl_2 mixture. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (95:5 CH_2Cl_2/MeOH) to afford 0.02 g of **3** (85%) as a yellow solid (mp 162 °C, hexane/EtOAc). FTIR (NaCl) ν 3400−2900 (br), 1668 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.4−1.7 (m, 4H), 2.01 (s, 3H), 2.2−2.4 (m, 4H), 2.39 (s, 3H), 5.83 (s, 1H), 5.94 (br s, 1H), 6.08 (d, J = 11.7 Hz, 1H), 6.26 (d, J = 15.3 Hz, 1H), 6.41 (d, J = 15.8 Hz, 1H), 6.76 (d, J = 15.8 Hz, 1H), 7.18 (dd, J = 15.3, 11.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 13.4, 20.6, 21.9, 22.0, 24.0, 25.6, 119.3, 121.3, 128.7, 129.5, 131.7, 134.5, 134.7, 135.9, 137.4, 151.7, 167.7 ppm. HRMS (EI^+) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1626.

Ethyl (2*E*,4*E*,6*Z*,8*E*)-9-(6-Methylcyclohex-1-en-1-yl)-3,7-dimethylnona-2,4,6,8-tetraenoate (29). According to the general procedure described above for the one-pot Shapiro−Suzuki reaction, hydrazone **25**[27a,28] (0.15 g, 0.38 mmol) was treated with *n*-BuLi (0.37 mL, 3.0 M in hexane, 1.14 mmol), followed by $B(Oi\text{-}Pr)_3$ (0.17 mL, 0.75 mmol) and iodide **19** [previously generated from stannane **10** (0.15 g, 0.30 mmol)]. After stirring the mixture for 1 h at 25 °C, purification of the residue by column chromatography (SiO_2, 90:10 hexane/EtOAc) afforded **29** (0.08 g, 91%) as a yellow oil. (See Supporting Information for characterization data).

(2*E*,4*E*,6*Z*,8*E*)-9-(6-Methylcyclohex-1-en-1-yl)-3,7-dimethylnona-2,4,6,8-tetraenoic Acid (4). According to the general procedure described above for the hydrolysis of esters, **29** (0.03 g, 0.10 mmol) in ethanol (0.22 mL) was treated with a 5 M aqueous KOH solution (0.19 mL) and then refluxed for 30 min. Purification by chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH) afforded 0.02 g of **4** (95%) as a yellow solid (mp 92 °C, hexane/EtOAc). (See Supporting Information for characterization data).

2,2-Dimethylcyclohexanone 2,4,6-Triisopropylbenzenesulfonylhydrazone (26). Ketone **22** (0.40 g, 3.17 mmol) was added with vigorous stirring to a solution of finely powdered 2,4,6-triisopropylbenzenesulfonylhydrazine (0.95 g, 3.17 mmol) in MeOH (3.2 mL). The suspension dissolved upon addition of concentrated hydrochloric acid (0.03 mL), and the product started to crystalize. The reaction mixture was kept at −10 °C overnight. The product was filtered, washed with cold MeOH, and dried (25 °C, 0.5 mmHg) affording hydrazone **26** (0.97 g, 75%) as white crystals (mp 144 °C, MeOH). FTIR (NaCl) ν 3600−3100 (br), 1365 (w), 659 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 6H), 1.31 (d, J = 6.8 Hz, 18H), 1.2−1.6 (m, 6H), 2.0−2.2 (m, 2H), 2.96 (sept, J = 6.8 Hz, 1H), 4.24 (sept, J = 6.8 Hz, 2H), 7.21 (s, 2H), 7.32 (s, 1H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$) δ 21.2, 22.6, 23.5, 24.7, 25.9, 26.8, 29.7, 34.1,

39.0, 40.7, 123.4, 124.0, 151.2, 153.0, 164.2 ppm. HRMS (EI^+) calcd for $C_{23}H_{38}N_2O_2S$ 406.2654, found 406.2652.

Ethyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(6,6-dimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate (30). According to the general procedure described above for the one-pot Shapiro−Suzuki reaction, hydrazone **26** (0.15 g, 0.38 mmol) was treated with *n*-BuLi (0.37 mL, 3.1 M in hexane, 1.14 mmol), followed by $B(Oi\text{-}Pr)_3$ (0.17 mL, 0.75 mmol), and iodide **19** [previously generated from stannane **10** (0.15 g, 0.30 mmol)]. The reaction mixture was stirred for 1 h at 25 °C. Purification by column chromatography (SiO_2, 90:10 hexane/EtOAc) afforded **30** (0.09 g, 97%) as a yellow oil. (See Supporting Information for characterization data).

(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(6,6-dimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic Acid (5). According to the general procedure described above for the hydrolysis of esters, **30** (0.05 g, 0.18 mmol) in EtOH (0.40 mL) was treated with a 5 M aqueous KOH solution (0.32 mL) and then refluxed for 30 min. The residue was purified by chromatography on silica gel (95:5 CH_2Cl_2/MeOH) to afford 0.05 g of **5** (92%) as a yellow solid (mp 135 °C, hexane/EtOAc). (See Supporting Information for characterization data).

2,6-Dimethylcyclohexanone Hydrazone (31). According to the general procedure described above for the preparation of hydrazones, **31** was prepared from ketone **23** (1.0 g, 7.92 mmol) as a very thick pale yellow oil (0.95 g, 85%) whose ^1H NMR spectrum revealed the presence of a mixture of diastereoisomers in a 3:1 ratio. (See Supporting Information for characterization data).

1,3-Dimethyl-2-iodocyclohex-1-ene (32). According to the general procedure described above for the preparation of alkenyl iodides, hydrazone **31** (0.40 g, 2.85 mmol) was converted into iodide **32** (0.44 g, 65%), which was isolated as a pale yellow oil. (See Supporting Information for characterization data).

Ethyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6-dimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate (33). According to the general procedure described above for the Suzuki reaction, iodide **32** (0.18 g, 0.78 mmol) was treated with a solution of *t*-BuLi in pentane (0.94 mL, 1.7 M, 1.60 mmol) followed by $B(OMe)_3$ (0.17 mL, 1.53 mmol) and iodide **19** [in situ generated from stannane **10** (0.30 g, 0.60 mmol)] for 3 h at 25 °C, to afford **33** (0.17 g, 93%) as a yellow oil. (See Supporting Information for characterization data).

(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6-dimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic Acid (6). According to the general procedure described above for the hydrolysis of esters, **33** (0.04 g, 0.14 mmol) in EtOH (0.31 mL) was treated with a 5 M aqueous KOH solution (0.25 mL) and then refluxed for 20 min. The residue was purified by chromatography on silica gel (95:5 CH_2Cl_2/MeOH) to afford 0.03 g of **6** (86%) as a yellow solid (mp 95 °C, hexane/EtOAc). (See Supporting Information for characterization data).

Ethyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2-methylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate (36). A solution of $Pd_2(dba)_3$ (0.010 g, 0.011 mmol) in NMP (3.2 mL) was treated with $AsPh_3$ (0.03 g, 0.11 mmol). After stirring for 5 min, a solution of triflate **34**[11g,31,32] (0.1 g, 0.41 mmol) in NMP (0.6 mL) was added, followed, after 10 min, by a solution of stannane **10** (0.22 g, 0.45 mmol) in NMP (0.6 mL). The resulting mixture was stirred at 25 °C for 3 h. Saturated aqueous KF solution was added, and the mixture was stirred for 30 min and extracted with Et_2O (3×). The combined organic extracts were washed with H_2O and saturated aqueous KF solution, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 90:10 hexane/EtOAc) to afford 0.12 g (95%) of **36** as a yellow oil. (See Supporting Information for characterization data).

(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2-methylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic Acid (7). According to the general procedure described above for the hydrolysis of esters, **36** (0.04 g, 0.15 mmol) in EtOH (0.34 mL) was treated with a 5 M aqueous KOH solution (0.27 mL) and then refluxed for 30 min. The residue was purified by chromatography on silica gel (95:5 CH_2Cl_2/MeOH) to afford 0.04 g of **7** (90%) as a yellow solid (mp 187 °C, hexane/EtOAc). (See Supporting Information for characterization data).

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Supporting Information Available: Characterization data and copies of ^1H and ^{13}C NMR spectra for all new compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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