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The Suzuki Reaction in Stereocontrolled Polyene Synthesis: Retinol (Vitamin A), its 9- and/or 13-Demethyl Analogs, and Related 9-Demethyl-dihydroretinoids

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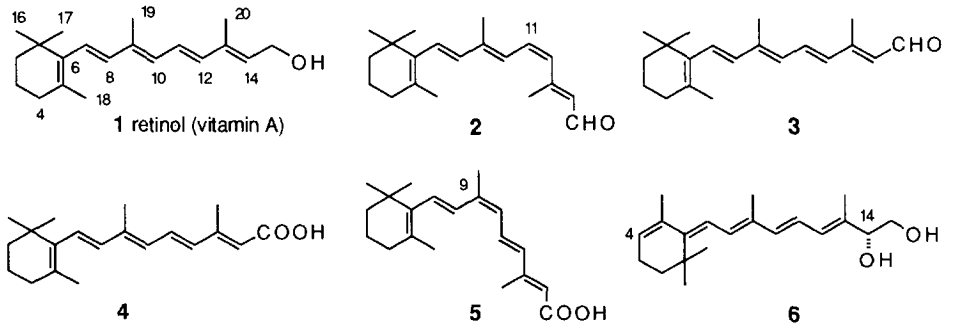
Abstract: A new synthesis of retinol (vitamin A) and 9- and/or 13-demethylretinols, with essentially complete control of regio- and stereochemistry, is described which is based on the thallium-accelerated, palladium-catalyzed cross-coupling reactions of (*E*)-1-alkenylboronic acids and (*E*)-1-alkenyl iodides (Suzuki reaction). The procedure has also been extended to the stereocontrolled synthesis of a series of 9-demethyl-dihydroretinoids of potential biological interest.

Organic compounds with polyolefinic structure are frequently found in living systems. Not unexpectedly, their ability to elicit a wide range of physiological effects stems oftentimes from changes in olefin configuration. A case in hand is the family of polyenes related to vitamin A (retinoids).[1,2] The parent vitamin A (**1**, Figure 1) is known to be involved in fetal development and in the regulation of proliferation and differentiation of cells throughout life.[3] Aldehydes derived from vitamin A (**1**) are the chromophores of retinal-binding proteins: 11-*cis*-retinal (**2**) in rhodopsin,[4a-d] and *trans*-retinal (**3**) in bacteriorhodopsin,[4d-j] the light-driven photosystem of *Halobacterium salinarium*. The biological responses of the proteins are triggered by double-bond isomerization of the chromophores upon light excitation. Most recently, retinoic acid (**4**) (a product of retinol metabolism and, in certain cells, synthesized from β-carotene[3]) and 9-*cis*-retinoic acid (**5**) have been characterized as the ligands for the retinoid family of ligand-inducible transcriptional activators (RARs and RXRs, respectively).[5] Finally, 14-hydroxy-4,14-*retro*retinol (**6**) (Figure 1), a metabolite of retinol (**1**), has been shown to mediate the growth of B-lymphocytes and other cell lines in a process which could constitute a new pathway for vitamin A activity.[6]

Figure 1

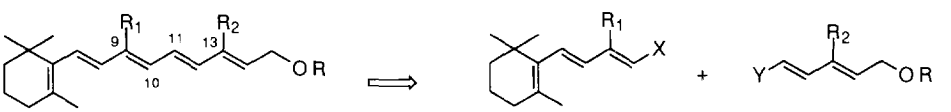


Considering the interplay between the stereochemistry of retinoids and their biological activities, any synthetic approach to these compounds must satisfy the requirement of sterochemical control, in order to obtain the desired isomer in a highly stereoselective manner. Despite the recent achievements in the preparation of conjugated (*E*/*Z*)-dienes and trienes using a variety of synthetic procedures, there is still a need for versatile and efficient approaches to higher unsaturated (*E*/*Z*)-polyolefins with controlable and uniform configuration.

In the retinoid field, the first industrial synthesis of vitamin A (**1**) by Isler[7a] at Hoffmann La Roche was followed by other approaches using olefin-forming reactions, some of them industrially exploited. These include Wittig condensations (at BASF[7b]), Julia's sulfone coupling (at Roche[7c] and Rhône-Poulenc[7d]) and a variety of recently disclosed double bond forming reactions such as reductive elimination of allylic diols,[8a] double elimination of β-alkoxysulfones,[8b] and dipolar cycloadditions.[8c] An alternative route to vitamin A is alkenyl-alkenyl coupling catalyzed by a transition metal. In a comprehensive study of the metal-catalyzed reactions of alkenyliodides and different alkenyl-metal derivatives, Negishi showed that organozinc[9a] compounds afforded the best yields of vitamin A (**1**). We also reported the palladium-catalyzed coupling of organoboron[9b,c] derivatives and alkenyliodides for the stereocontrolled preparation of 9-demethylretinoids and arotinoids.

We describe here a full account of this work, including the highly stereoselective preparation of vitamin A (**1**) and of the complete series of analogs with totally or partially demethylated side chains (**7-9**).[10] Our convergent approach to the retinoid structure[11] is based on disconnection of the C-10, C-11 bond (Scheme 1) at the centre of the side chain (also known as the $C_{14} + C_6$ route[11a]). For the transition metal-catalyzed cross-coupling of alkenylboronic acids and alkenyliodides,[12] two options are in principle feasible (Scheme 1), the choice of which moiety to derive from the boronic acid and which from the iodide depending upon relative ease of preparation.

Scheme 1



1, 7, 8, 9

(Scheme 2)

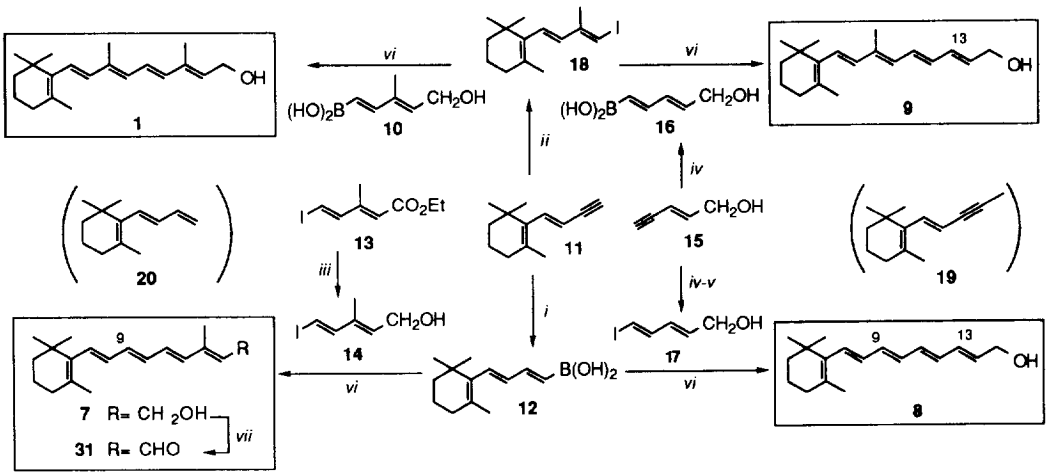
Highly Stereoselective Synthesis of Retinol and its 9- and/or 13-Demethyl Analogs

In the preparation of 9-demethylretinol (**7**) and 9,13-bisdemethylretinol (**8**), the choice of coupling partners is irrelevant, the overall process being a conjugated variant of Suzuki's classical diene synthesis.[12] The highly sensitive boronic acid partner could be either the boronic acid **10**[13] or the C_{13} boronic acid **12**[9b,c] already described (Scheme 2). As regards the alkenyliodide, **14** was prepared in 88% yield by DIBALH reduction of ester **13**[9b,c]; and **17** by iodine treatment[14] (I_2, NaOH, 0 °C, 62% yield) of alkenylboronic acid **16** obtained in 64% yield from alkyne **15** following the same procedure described[13c] for **10** (Scheme 2).

For the palladium-catalyzed cross-coupling reaction, the conditions developed by Kishi[15] on route to palytoxin proved to be compatible with the thermal instability of vitamin A and its derivatives. As a

representative example, stirring a degassed THF solution of **12** (1.5 equiv, obtained[9c] by hydroboration of **11**[16], followed by hydrolysis) and **14** or **17** (1.0 equiv) in the presence of 10% aqueous TlOH (4.5 equiv) and $Pd(PPh_3)_4$ (0.1 equiv) for 30 minutes at room temperature, followed by filtration, standard work-up and purification, afforded 9-demethylretinol (**7**) and 9,13-bisdemethylretinol (**8**) in respectively 50% and 40% yields (Scheme 2).

Scheme 2



Scheme 2. Reagents and reaction conditions
i. 1. Catecholborane, BH_3.N,N-diethylaniline (10%), benzene, rt, 9 h, 74%. 2. H_2O, rt, 2h. *ii.* 1. Me_3Al, Cl_2ZrCp_2, CH_2Cl_2, 0 °C to rt, 12h. 2. ICN, THF, 0 °C, 0.5 mL/h, 72%. *iii.* DIBALH, THF, 0 °C, 2 h, 88%. *iv.* 1. Catecholborane (2 equiv), 0 °C to rt, 2 h. 2. H_2O, rt, 2.5 h, 64 %. *v.* I_2, NaOH, Et_2O, 0 °C, 62%. *vi.* $Pd(PPh_3)_4$ (0.1 equiv), 10% aq. TlOH (4.5 equiv), THF, 83% for **1**, 50% for **7**, 40% for **8**, and 60% for **9**. *vii.* MnO_2, CH_2Cl_2, rt, 1h, 90%.

In the case of retinol (**1**) and its 13-demethyl derivative (**9**), the preparation of a C_{14} boronic acid related to **12** from a terminal alkyne such as **11** would require the incorporation of a methyl group and a boron at neighbouring positions (Scheme 1). For the so-called terpenoid structure, the required regio- and stereoselective carboboration of terminal alkynes presents obvious difficulties; the literature on carbometallation of alkynes[17] includes only one report of carboboration (with BBr_3 followed by a palladium-catalyzed reaction with an organozinc).[18] We therefore explored the possibility of substituting boron for aluminum on precursors already possessing the required methyl group. However, although carboalumination of alkynes in the presence of Cl_2ZrCp_2 has been successfully followed by metallation of the organoalane intermediate in several reported synthesis,[19] we were unsuccessful in our efforts to use a boron electrophile to trap the aluminate complex obtained upon treatment of a putative alane with an alkyllithium. We accordingly decided to use the carboalumination of alkynes for the preparation of the iodide partner. Alkenyliodide **18** was obtained by zirconium-mediated methylalumination[9a] and subsequent Al-I exchange by slow addition of a solution of ICN in THF at 0 °C. The moderate yield (72%, considerably higher than using alternative iodine sources, such as I_2[9a] or N-iodosuccinimide) in the preparation of the iodide **18** is partly due to the lack of regioselectivity on the addition of the reagent to alkyne **11**. Methylated alkyne **19** (Scheme 2) is observed in the reaction mixture, albeit in low yield (5-10%). The reported[20] rate acceleration by addition of 1.5 equivalents of H_2O to the carboalumination

reagent at -20 °C did not improve the yield of **18**. Finally, Uenishi's recently reported[21a] double metalation (with Sn and Cu, as described by Nozaki[21b,c]) followed by trapping with electrophiles (methyl iodide and iodine, in that order) led to an incomplete conversion of alkyne **11** to iodide **18**, although no secondary products were observed.

Suzuki coupling of **10** or **16** with **18** went uneventfully, requiring 12 h to reach completion and affording, after purification, retinol (**1**) and 13-demethylretinol (**9**) in 83% and 60% yields, respectively, with retention of the geometries of the coupling partners (Scheme 2). Despite the stability of alkenylboronic acids to basic aqueous conditions, some of the reaction mixtures from the Suzuki coupling contained minor amounts (5-10%) of triene **20** (Scheme 2) which is likely to have arisen by a rapid protodeboronation[22] competing under the reaction conditions.

The demethylretinols **7-9** are used in mechanistic studies aiming to clarify the key isomerohydrolase-catalyzed endothermic step in the back-reactions of the vertebrate visual cycle, i.e., the formation of 11-*cis*-retinol and a fatty acid from *trans*-retinyl esters;[10] the results of incubating the vitamin A analogs with retinal pigment epithelium have ruled out an isomerization mechanism based on proton abstraction at certain allylic positions accompanying hydrolysis of the retinyl esters.[10] Esters of 9-demethylretinol are substrates for the isomerohydrolase acting on the back-reactions of the visual cycle, which suggests that hydrogen abstraction at that position could be a feasible mechanism for the endergonic conversion of *trans*-retinyl esters to 11-*cis*-retinol.[10]

Stereocontrolled Synthesis of 9-Demethylretinoids

In addition to the above, other 9-demethylretinoids have been used to clarify key steps of the vertebrate visual cycle involving 11-*cis*-retinal to *trans*-retinal interconversions. It has been shown that pigments derived from 11-*cis*-9-demethylretinal (**30**) (Scheme 3) fail to produce the biochemically active form of rhodopsin (meta II) upon photoisomerization, thus leading to the suggestion that the non-bonding interactions of the C-9-methyl group of 11-*cis*-retinal (**2**) with protein residues triggers the isomerization of a peptide bond adyacent to a proline necessary for the activation of the G-protein.[23a,b]

A recent report on the regeneration of bacteriorhodopsin with *trans*-9-demethylretinal (**31**) (Scheme 2) further highlights the role of the steric interactions between protein and chromophore on the functioning of the pigment. Compare to the native pigment, the photocycle of bacteriorhodopsin regenerated with *trans*-9-demethylretinal (**31**) is slower, the half-life of the intermediates is altered, and the reisomerization of the chromophore is affected, which is likely due to reduced protein-chromophore steric interactions.[23c]

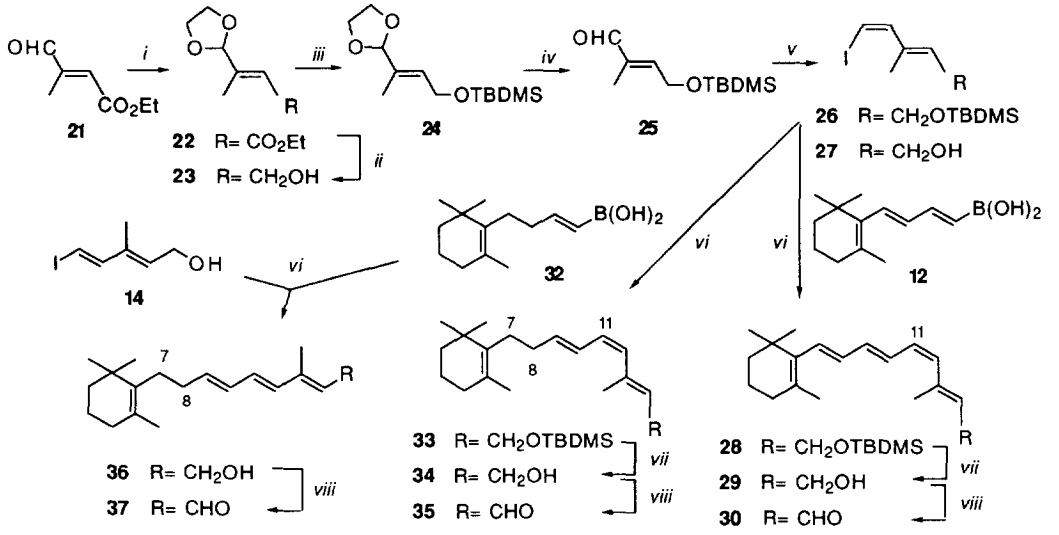
In order to provide useful retinoids for additional bioorganic studies, we also describe the stereochemically controlled preparation of 9-demethylretinoids and a series of derivatives modified by saturation of double bonds in the hydrophobic terminus.

The stereocontrolled preparation of 9-demethylretinoids with either 11-*cis* or *trans* geometries follows the same methodology already described for the parent 9-demethylretinol (**7**), namely Suzuki coupling of boronic acid **12** and alkenyliodide **14**. The stereoselectivity could be assesed by reaction of the same boronic acid **12** with the alkenyliodide of opposite stereochemistry at the reacting olefin. Scheme 3 depicts the highly stereoselective synthesis of the (*Z*)-iodide **26**, starting from ethyl (*E*)-3-formylbut-2-enoate **21**. Protection of the aldehyde as acetal (ethylene glycol, PPTS, benzene, 91%) was followed by reduction of **22** with LAH at 0 °C to afford **23** (80%). Hydrolysis of the acetal protecting group at this stage

proved incompatible with the free alcohol group (formation of furane derivatives was observed), which required the protection of the latter as silyl ether **24** (TBDMSCl, Imidazole, DMF, rt, 96%) before deprotection of the acetal (*p*-TsOH, H_2O, 99%) to afford the required aldehyde **25**. Treatment of **25** with iodomethyltriphenylphosphonium iodide under Stork's conditions[24] (sodium hexamethyldisilazide, THF, HMPA, -80 °C) afforded alkenyliodide **26** as a 16:1 mixture of *Z/E* stereoisomers (91%). Deprotection of the silyl group was accompanied by a facile isomerization to the most stable iodoolefin (a 5:1 mixture of *Z/E* stereoisomers of alcohol **27** was obtained). Accordingly, protected electrophile **26** was selected for the Suzuki coupling to the boronic acids.

Treating boronic acid **12** (1.25 equiv) and alkenylidodide **26** (1.0 equiv) in THF in the presence of 10% aqueous TlOH (3.85 equiv) and $Pd(PPh_3)_4$ (0.1 equiv) as described for **7** afforded protected (11Z)-9-demethylretinol **28** in 63% yield with essentially complete retention of the stereochemistry of the reaction partners. Fluoride-induced deprotection of the silyl ether **28** provided (11Z)-9-demethylretinol **29** in 71% yield (Scheme 3).

Scheme 3



Scheme 3. Reagents and reaction conditions

i. Ethylene glycol, PPTS, benzene, reflux, 4h, 91%. *ii.* LAH, ether, 0 °C, 45 min, 80%. *iii.* Imidazole, TBDMSCl, DMF, rt, 90 min, 96%. *iv.* *p*-TsOH.H_2O, acetone-H_2O, 15 min, 99%. *v.* ICH_2PPh_3I, $NaN(TMS)_2$, HMPA, -78 °C to rt, 3h, 91%. *vi.* $Pd(PPh_3)_4$ (0.1 equiv), 10% aq. TlOH (3.85 equiv), THF, 30 min, 63% for **28**, 58% for **33**, and 51% for **36**. *vii.* TBAF, THF, rt, 4h, 71% for **29** and 56% for **34**. *viii.* MnO_2, CH_2Cl_2, rt, 1h, 89% for **30**, 91% for **35**, and 81% for **37**.

The synthesis described above for **7** and **28** constitutes the first sterecontrolled preparation of 9-demethylretinoids.[9b] Alternative syntheses[25] used variations of the Wittig reaction, thus affording mixtures of products, which were derivatized (as acetates or aldehydes, *vide infra*) due to the instability of the 9-demethylretinols **7** and **29**. Alcohols **29** and **7** were treated with MnO_2 in CH_2Cl_2 at room temperature for 12 hours to obtain the corresponding retinals **30** (Scheme 3) and **31** (Scheme 2) in 89% and 90% yields,

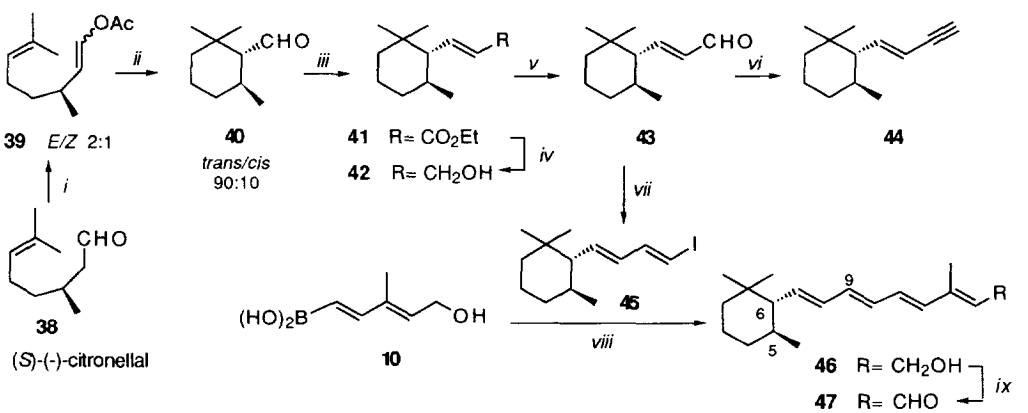
respectively. Spectroscopic data for **30** and **31** are identical with those described for the same compounds alternatively obtained.[25d,e]

Following the described protocol, the coupling of boronic acid **32**[9c] to alkenyl iodide **26** in the presence of $Pd(PPh_3)_4$ and 10% aqueous TlOH following Kishi's conditions, afforded (11Z)-9-demethyl-7,8-dihydroretinyl-*tert*-butyldimethylsilyl ether **33** in 58% yield. Deprotection with TBAF gave (11Z)-9-demethyl-7,8-dihydroretinol **34** in 56% yield. Likewise, coupling of boronic acid **32** and alkenyliodide **14** under the same conditions provided 9-demethyl-7,8-dihydroretinol **36** in 51% yield (Scheme 3).

Retinols **34** and **36** were individually treated with MnO_2 as described above to afford retinals **35** and **37** in 91% and 81% yield, respectively. Measurement of the coupling constants on the ^1H NMR spectra of these and other pairs of retinoid isomers described in this work supported the assignment of the geometry for the newly formed C-10, C-11 bond. Values of $J_{11,12}$ = 11.5 Hz and $J_{11,12}$= 15.3 Hz for **35** and **37** were indicative of the (11*Z*) and (11*E*) configuration, respectively.

For the preparation of the remaining member of the series, the *trans*-5,6-dihydro analogs, the required cyclohexane ring was obtained by acid-catalyzed cyclization of the enolacetate derived from (*S*)-(-)-citronellal **38**, reaction already described for the optically inactive material.[26] Treatment of (*S*)-(-)-citronellal **38** with a mixture of acetic anhydride, triethylamine and potassium acetate at 120 °C for 4h, followed by distillation gave the enol acetate **39** in 89% yield as a 2:1 mixture of olefin isomers.[26] Acid-induced (85% H_3PO_4) cyclization[26] of **39** afforded the aldehyde **40** in 50% yield as a 90:10 *trans/cis* mixture. Vinylogous aldehyde **43** was obtained by the three-step sequence shown on Scheme 4. Condensation of **40** with triethyl phosphonoacetate in DMF using NaOEt as base provided unsaturated ester **41** (67%), which was reduced with LAH (98%) and the resulting alcohol **42** was oxidized with MnO_2 (81%) to enal **43**. Separation of the 90:10 *trans/cis* mixture of aldehydes **43** was conveniently achieved at this stage by column chromatography.

Scheme 4



Scheme 4. Reagents and reaction conditions

i. Ac_2O, Et_3N, KOAc, 120 °C, 4h, 89%. *ii.* 85% H_3PO_4, 100 °C, 12h, 50%. *iii.* $(EtO)_2(O)PCH_2COOEt$, NaOEt, DMF, 0 °C to rt, 12h, 67%. *iv.* LAH, ether, 0 °C, 5h, 98%.*v.* MnO_2, CH_2Cl_2 , rt, 12h, 81%. *vi.* ICH_2PPh_3I, KO*t*-Bu, THF, -78 °C, 2h, then rt, 88%. *vii.* $CrCl_2$, CHI_3,THF, 0 °C; then rt, 3h, 89%. 2. NaOH, n-BuOH, reflux, 5h, 60%. *viii.* $Pd(PPh_3)_4$ (0.1 equiv), 10% aq. TlOH (3.85 equiv), THF, 12h, 70%. *ix.* MnO_2, CH_2Cl_2, rt, 1h, 99%.

For the preparation of the required boronic acid, alkyne **44** was obtained from aldehyde **43** (88% yield) using a Wittig reaction with iodomethyltriphenylphosphonium iodide in the presence of excess KO*t*-Bu,[27a] occasionally used as an alternative to the Corey-Fuchs procedure.[27b] Despite the structural similarity with other members of the series, alkyne **44** resisted a variety of hydroboration conditions, either using catecholborane (Brown's hydroboration in benzene at reflux temperatures,[28a] catalyzed by the BH_3.N,N-diethylaniline complex[28b] and Roush's modification[13c]) or the more recently developed pinacolborane,[28c] generated *in situ* from $Me_2S.BH_3$ (2 equivalents) and pinacol (2 equivalents) in CH_2Cl_2. Therefore, we decided to exchange the functionality on the coupling partners. Dienyliodide **45** could easily be obtained from aldehyde **43** by reaction with iodoform in the presence of $CrCl_2$.[29] In contrast to unsaturated aldehyde **21** (which is conjugated to an ester, and gives iodide **13**, Scheme 2, with high stereoselectivity[9b]) aldehyde **43** furnished, as shown by ^1H NMR, a 4:1 mixture of *(E/Z)*-iodides **45** in 89% yield. Without separation, the mixture was treated with NaOH in refluxing n-butanol[30] for 5 h to afford stereochemically pure (*E*)-iodide **45** in 60% yield (Scheme 4).

Coupling of iodide **45** and boronic acid **10** under the described conditions for 12 h afforded, after purification, (5*S*,6*S*)-9-demethyl-5,6-dihydroretinol **46** in 70% yield. Similar to other analogs, retinol **46** proved to be extremely unstable, and showed extensive decomposition even after storage under argon at -78 °C. Accordingly, it was oxidized to aldehyde **47** (Scheme 4) immediately after purification.

For the preparation of the (11*Z*)-isomer of compound **46**, we unsuccessfully tried a series of halogen-metal exchange reactions on iodide **45**. However, treatment of **45** with a variety of lithium bases followed by trapping the organolithium with $B(OMe)_3$ gave the corresponding boronic acid in low yield, after hydrolysis. We are currently trying to develop an efficient synthesis of conjugated (*Z*)-dienylboronic acids.[31]

To summarize, we have described the highly stereoselective synthesis of vitamin A, the 9- and/or 13-demethylretinols, and a series of 9-demethylretinoids from readily accesible alkenyl fragments. Since the compounds constitute good test cases due to their instability, we are confident that the excellent chemo-, regio- and stereoselectivities and homo/cross discrimination of alkenyliodide-alkenylboronic acid coupling (comparable to those of alkenylzinc coupling[9a]) will allow significant advances in the stereocontrolled construction of polyenes of biological interest, a goal currently pursued in our laboratories.

EXPERIMENTAL SECTION

General Experimental Procedures

Procedures. All reactions were performed under a positive pressure of dry argon in oven and/or flame-dried glassware. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannula through a rubber septum. Cooling was performed using ice-water (0 °C) or dry ice-acetone (-60 °C and -78 °C). All reactions and manipulations involving retinoids as final products or starting materials were carried out under subdued red light.

Physical Data. Melting points were measured with a capillary melting point apparatus and are uncorrected. Bulb-to-bulb distillations were carried out on a Büchi GKR-50 Kugelrohr; boiling points refer

to air bath temperatures and are uncorrected. Optical rotations were determined in ethanol solution on a JASCO Digital Polarimeter DIP 370 equipped with a sodium lamp source. Proton magnetic resonance spectra (^{1}H NMR) were recorded on either a Bruker WM-250 (250 MHz) or Bruker AMX300 (300 MHz) spectrometer as noted at ambient temperature. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane, or in ppm relative to the singlet at 7.26 ppm for chloroform-*d*, 7.20 ppm for benzene-d_6 or 4.90 ppm for CD_3OD; coupling constants J are reported in hertzs and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets etc...), coupling constant (hertz), and peak assignment). Carbon magnetic resonance spectra (^{13}C NMR) were recorded on either a Bruker WM-250 (63 MHz) or Bruker AMX300 (75 MHz) spectrometer. Spectra were referenced to $CDCl_3$ (77.0 ppm), C_6D_6 (128.0 ppm) or CD_3OD (49.0 ppm). Routine ^{13}C NMR spectra were fully decoupled by broad-band decoupling. Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet) and peak assignment). Multiplicities were assigned with the aid of the DEPT pulse sequence. Infrared spectra (IR) were recorded in 0.1 mm path length sodium chloride cavity cells on Perkin Elmer 1420 or MIDAC Prospect FTIR spectrometers. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Bands are caracterized as follows: s = strong, m = medium, w = weak, or br = broadened. Samples were typically prepared as films by evaporating a sample solution on a salt plate or in $CHCl_3$ solution. UV spectra were recorded on a Hewlett-Packard HP8452A UV-VIS spectrophotometer. Low-resolution mass spectra (MS) were measured on a Hewlett-Packard 59970-GC/MS system (70 eV). High-resolution mass spectra data (HRMS) were recorded on a Kratos MS-50 instrument at an ionizing current of 98 mA and an ionizing voltage of 70 eV. Significant fragments are reported as follows: *m/z* (intensity relative to base = 100), with accurate mass reported for the molecular ion (M^+) or suitable fragment ion. Standard deviation was determined as σ= 1.6 ppm.

Chromatography. Analytical thin-layer chromatography was performed on 0.25 mm Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light, and by staining with iodine or a 15 % ethanolic phosphomolybdic acid solution. Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh). High-performance liquid chromatography (HPLC) was performed with a Waters 510 liquid chromatograph equipped with a μPorasil column.

Solvents and Reagents. Solvents were distilled and/or stored over molecular sieves 4 Å prior to use. Dichloromethane, triethylamine, hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled from calcium hydride; ether and tetrahydrofuran (THF) from sodium benzophenone ketyl. "Brine" refers to saturated aqueous solution of NaCl. Tetrakistriphenylphosphine palladium (0) was prepared according to the Inorganic Synthesis procedure.[32] All other reagents were used as obtained from commercial sources or purified according to standard procedures.[33]

(*E,E*)-5-Iodo-3-methylpenta-2,4-dien-1-ol (14). To a solution of ester **13**[9b,c] (0.21 g, 0.79 mmol) in THF (4 mL) was slowly added DIBALH (1.56 mL, 1.0 M in hexane, 1.56 mmol) at 0 °C and the mixture was stirred for 2 h, before being quenched by careful addition of water. The aqueous layer was extracted with ether (3 x 20 mL) saturated with NaCl and re-extracted with ether (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by chromatography on

silica gel (80:20 hexane/ethyl acetate) to afford 0.156 g (88%) of compound **14** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77 (3H, s, C_3-CH_3), 4.26 (2H, d, J= 6.7 Hz, $2H_1$), 5.65 (1H, t, J= 6.7 Hz, H_2), 6.33 (1H, d, J= 14.7 Hz, H_5), 7.07 (1H, d, J= 14.7 Hz, H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0 (q, C_3-CH_3), 59.0 (t, C_1), 76.0 (d, C_5), 131.4 (d, C_2), 136.4 (s, C_3), 148.8 (d, C_4). MS m/z (%): 224 (M^+, 100), 181 (5), 153 (5), 127 (29), 97 (95), 79 (33), 77 (30), 69 (46), 53 (25). HRMS: Calcd. for C_6H_9IO: 223.9700. Found: 223.9701.

[(*E*,*E*)-5-Hydroxypenta-1,3-dien-1-yl]boronic Acid (16). Doubly distilled catecholborane (0.82 mL, 7.68 mmol) was slowly added (20-25 min) to alkyne **15** (0.30 g, 3.66 mmol) placed in a Schlenk flask at 0 °C under argon, allowing for slow release of hydrogen. The reaction flask was closed and stirred at rt for 2 h, observing the formation of a yellow solid. The reaction mixture was kept at -20 °C for 16 h, then cold water (7 mL) was added, and the resulting white suspension was stirred at rt for 2.5 h. The mixture was saturated with NaCl and extracted with ethyl acetate (5 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed to afford a residue which was purified by chromatography on silica gel (elution gradient: from 50:50 hexane/ethyl acetate - to remove the catechol- to 95:5 Cl_2CH_2/MeOH) to afford 0.30 g (64%) of compound **16** which was used in the next step without further purification. ^{1}H NMR (250 MHz, CD_3OD): δ 4.15 (2H, d, J= 5.2 Hz, $2H_5$), 5.72 (1H, d, J= 17.3 Hz, H_1), 5.98 (1H, dt, J= 14.9, 5.2 Hz, H_4), 6.37 (1H, dd, J= 14.9, 10.7 Hz, H_3), 6.98 (1H, dd, J= 17.3, 10.7 Hz, H_2). ^{13}C NMR (63 MHz, CD_3OD): δ 63.2 (t, C_5), 133.7 (d), 137.6 (d, 2x), 149.6 (d). MS m/z (%): 117 (100), 89 (57), 77 (16), 75 (81), 73 (96), 58 (36).

(*E*,*E*)-5-Iodopenta-2,4-dien-1-ol (17). To a solution of boronic acid **16** (35 mg, 0.27 mmol) in ether (1.5 mL) at 0 °C was added sequentially 3N aq. NaOH (0.25 mL, 0.75 mmol) then a solution of I_2 (77 mg, 0.30 mmol) in ether (2.5 mL). The resulting mixture was stirred at 0 °C for 15 min and the excess iodine was quenched by addition of a saturated $Na_2S_2O_3$ solution. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic extracts were washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), dried over $MgSO_4$, and evaporated to dryness. The residue was purified by chromatography on silica gel (75:25 hexane/ethyl acetate) to afford 35 mg (62%) of compound **17** as a white solid (m.p. 37 °C, hexane-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (2H, br, $2H_1$), 5.84 (1H, dt, J= 15.2, 5.3 Hz, H_2), 6.19 (1H, dd, J= 15.2, 10.7 Hz, H_3), 6.34 (1H, d, J= 14.4 Hz, H_5), 7.04 (1H, dd, J= 14.4, 10.7 Hz, H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.9 (t, C_1), 79.9 (d, C_5), 130.8 (d), 133.3 (d), 144.7 (d). IR ($CHCl_3$): υ 3600 (m, free OH), 3600-3300 (br, H-bonded OH), 3050 (w, C-H), 3010 (s, C-H), 1380 (m), 1260 (m), 1170 (m), 1080 (s, C-O), 980 (s) cm^{-1}. MS m/z (%): 210 (M^+, 26), 167 (30), 149 (100), 127 (I^+, 15), 111 (20), 97 (28), 95 (23), 85 (23), 83 (M^+-I, 50), 81 (30), 71 (32), 69 (45), 57 (43), 55 (54). HRMS: Calcd. for C_5H_7IO: 209.9544. Found: 209.9550.

Ethyl (*E*)-4,4-Ethylenedioxy-3-methylbut-2-enoate (22). A solution of aldehyde **21** (19.08 g, 0.13 mol), ethylene glycol (12.5 g, 0.20 mol) and PPTS (3.77 g, 0.015 mol) in benzene (250 mL) was heated to reflux under a Dean-Stark trap for 4 h. Upon cooling, brine was added, the layers were separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (98:2

CH_2Cl_2/MeOH) to afford 22.67 g (91%) of compound **22** (colorless oil; b.p. 75 °C/0.5 mm Hg). ^1H NMR (250 MHz, $CDCl_3$): δ 1.28 (3H, t, J= 7.1 Hz, $OCH_2\underline{CH_3}$), 2.11 (3H, d, J= 1.3 Hz, C_3-CH_3), 3.9-4.0 (4H, m, OCH_2CH_2O), 4.17 (2H, q, J= 7.1 Hz, $O\underline{CH_2}CH_3$), 5.19 (1H, s, H_4), 6.01 (1H, s, H_2). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.1 (q), 14.3 (q), 60.0 (t), 65.5 (t, 2x), 105.1 (d), 118.5 (d), 152.8 (s), 166.2 (s). IR ($CHCl_3$): υ 2980 (s, C-H), 2890 (s, C-H), 1710 (s, C=O), 1660 (s, C=C) cm^{-1}. MS m/z (%): 157 (M^+-Et, 14), 141 (20), 113 (23), 73 (100), 69 (21). HRMS: Calcd. for $C_9H_{14}O_4$: 186.0892. Found: 186.0892.

(*E*)-4,4-Ethylenedioxy-3-methylbut-2-en-1-ol (23). Acetal **22** (10.0 g, 0.05 mol) in ether (50 mL) was added via cannula to a solution of $LiAlH_4$ (2.46 g, 0.06 mol) in ether (150 mL) at 0 °C. The resulting suspension was stirred for 45 min before carefully being quenched with water. NaCl was added to the mixture, which was extracted with ether (4 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Distillation of the residue (88 °C/1 mm Hg) afforded compound **23** (6.23 g, 80%) as a colorless oil. ^1H NMR (250 MHz, C_6D_6): δ 1.68 (3H, s, C_3-CH_3), 3.4-3.6 (4H, m, OCH_2CH_2O), 4.04 (2H, br, $2H_1$), 5.10 (1H, s, H_4), 5.87 (1H, t, J= 6.7 Hz, H_2). ^{13}C NMR (63 MHz, C_6D_6): δ 10.5 (q, C_3-CH_3), 58.8 (t, C_1), 65.1 (t, 2x), 107.1 (d, C_4), 130.6 (d, C_2), 134.4 (s, C_3). IR ($CHCl_3$): υ 3600-3200 (br, O-H), 2960 (s, C-H), 2890 (s, C-H) cm^{-1}. HRMS: Calcd. for $C_7H_{12}O_3$: 144.0787. Found: 144.0800.

(*E*)-*tert*-Butyldimethylsilyl-(4,4-Ethylenedioxy-3-methylbut-2-en-1-yl) Ether (24). Imidazole (1.43 g, 0.021 mol) and *tert*-butyldimethylsilyl chloride (3.16 g, 0.021 mol) were added sequentially to a solution of alcohol **23** (2.90 g, 0.02 mol) in DMF (60 mL). After stirring at rt for 90 min, water and hexane were added and the aqueous layer was extracted with hexane. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford compound **24** (5.0 g, 96%) which was purified by fractional distillation (85 °C/0.5 mm Hg). ^1H NMR (300 MHz, C_6D_6): δ 0.11 (6H, s, Si-$2CH_3$), 1.02 (9H, s, Si-*t*-Bu), 1.73 (3H, s, C_3-CH_3), 3.4-3.6 (4H, m, OCH_2CH_2O), 4.26 (2H, d, J= 5.8 Hz, $2H_1$), 5.14 (1H, s, H_4), 6.00 (1H, t, J= 5.8 Hz, H_2). ^{13}C NMR (75 MHz, C_6D_6): δ -4.8 (q, Si-$2CH_3$), 11.0 (q, C_3-CH_3), 18.6 (s, Si-C), 26.3 (q, Si-*t*-Bu), 60.2 (t), 65.4 (t, 2x), 107.3 (d, C_4), 131.0 (d, C_2), 133.7 (s, C_3). IR ($CHCl_3$): υ 3020 (s, C-H), 2950 (s, C-H), 2880 (s, C-H), 1670 (m, C=C), 1470 (m) cm^{-1}. MS m/z (%): 257 (M^+-1, 1), 233 (2), 219 (1), 189 (3), 147 (12), 113 (12), 103 (13), 83 (100), 75 (92), 73 (62), 57 (7), 55 (19). HRMS: Calcd. for $C_{13}H_{26}O_3Si$: 258.1651. Found: 258.1654.

(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-methylbut-2-enal (25). To a solution of acetal **24** (5.0 g, 0.02 mol) in acetone (200 mL) were added *p*-TsOH.H_2O (0.36 g, 1.90 mmol) and water (5 mL) and the resulting solution was stirred for 15 min. Addition of a cold saturated aqueous $NaHCO_3$ solution was followed by extraction with $CHCl_3$. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and concentrated to afford 4.11 g (99%) of compound **25**, which was purified by fractional distillation (58 °C/0.5 mm Hg). ^1H NMR (250 MHz, $CDCl_3$): δ 0.07 (6H, s, Si-$2CH_3$), 0.89 (9H, s, Si-*t*-Bu), 1.70 (3H, s, C_2-CH_3), 4.48 (2H, d, J= 5.3 Hz, $2H_4$), 6.49 (1H, t, J= 5.3 Hz, H_3), 9.39 (1H, s, H_1). ^{13}C NMR (63 MHz, $CDCl_3$): δ -5.4 (q, Si-$2CH_3$), 9.2 (q, C_2-CH_3), 18.2 (s, Si-C), 25.7 (q, Si-*t*-Bu), 60.4 (t, C_4), 137.8 (s, C_2), 152.9 (d, C_3), 194.4 (d, C_1). IR ($CHCl_3$): υ 2960 (s, C-H), 2930 (s, C-H), 2860 (s, C-H), 1685 (s, C=O), 1205 (m), 1110 (m) cm^{-1}. MS m/z (%): 157 (M^+-*t*-Bu, 18), 111 (3), 97 (3), 75 (100), 73 (13), 57 (10). HRMS: Calcd. for $C_{11}H_{22}O_2Si$: 214.1389. Found: 214.1380.

tert*-Butyldimethylsilyl-[(2*E*,4*Z*)-5-Iodo-3-methylpenta-2,4-dien-1-yl] Ether (26).** To a suspension of iodomethyltriphenylphosphonium iodide (0.56 g, 1.05 mmol) in THF (10 mL) was added sodium hexamethyldisilazide (1.05 mL, 1.0 M in THF, 1.05 mmol) at rt. The resulting solution was stirred for 5 min, cooled down to -60 °C and HMPA (0.22 mL, 1.264 mmol) was then added. After cooling to -78 °C, a solution of aldehyde **25** (0.18 g, 0.84 mmol) in THF (4 mL) was added via cannula. The resulting mixture was stirred at rt for 3 h. After adding hexane (20 mL), the mixture was washed with brine (2 x 20 mL) and water (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (99:1 hexane/pyridine) to afford 0.26 g (91%) of compound **26** as a yellow oil. The ^1H NMR spectrum revealed a 16:1 mixture of 4*Z*/4*E* stereoisomers. Data for isomer **4*Z : ^1H NMR (250 MHz, $CDCl_3$): δ 0.09 (6H, s, Si-2CH_3), 0.91 (9H, s, Si-*t*-Bu), 1.89 (3H, s, C_3-CH_3), 4.28 (2H, d, J= 6.1 Hz, $2H_1$), 5.78 (1H, t, J= 6.1 Hz, H_2), 6.19 (1H, d, J= 8.5 Hz, H_4), 6.76 (1H, d, J= 8.5 Hz, H_5). ^{13}C NMR (63 MHz, C_6D_6): δ -4.7 (q, Si-2CH_3), 16.1 (q, C_3-CH_3), 18.7 (s, Si-C), 26.3 (q, *t*-Bu), 60.4 (t, C_1), 76.4 (d, C_5), 133.5 (s, C_3), 134.5 (d, C_2), 141.9 (d, C_4). IR ($CHCl_3$): υ 2960 (s, C-H), 2930 (s, C-H), 2860 (s, C-H), 1460 (m), 1255 (m), 1105 (s), 1055 (s) cm^{-1}. MS m/z (%): 337 (M^+-1, 6), 297 (36), 295 (15), 221 (15), 185 (34),181 (20), 170 (22), 127 (17), 95 (36), 89 (48), 75 (100), 73 (53), 57 (55). HRMS: Calcd. for $C_{12}H_{23}IOSi$: 338.0564. Found: 338.0564.

2-[(*E*,*E*)-4'-Iodo-3'-methylbuta-1',3'-dien-1'-yl]-1,3,3-trimethylcyclohexene (18) and 1,3,3-Trimethyl-2-[(*E*)-pent-1'-en-3'-yn-1'-yl]cyclohexene (19). To a suspension of Cl_2ZrCp_2 (92 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) was added trimethylaluminium (0.09 mL, 0.95 mmol) at 0 °C. To the resulting yellow solution was slowly added alkyne **11**[16] (55 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) at rt via cannula. The mixture was stirred at rt for 24 h, and then cooled to 0 °C before addition of a solution of ICN (155 mg, 0.95 mmol) in THF (2 mL) with a syringe pump at a rate of 0.5 mL/h. After adding 1.5 mL of a 1:1 THF/H_2O mixture, the product was extracted with ether. The organic layer was washed with aq. $Na_2S_2O_3$ solution and water, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (SiO_2, hexane) to afford 6 mg (10%) of alkyne **19** and 72 mg (72%) of iodide **18**,[9a] an unstable oil which quickly darkened. Data for **18**: ^1H NMR (300 MHz, C_6D_6): δ 1.06 (6H, s, C_3-2CH_3), 1.4-1.6 (4H, m, $2H_4$ and $2H_5$), 1.67 (3H, s, C_1-CH_3), 1.91 (3H, s, C_3'-CH_3), 1.95 (2H, m, $2H_6$), 6.04 (1H, d, J= 16.0 Hz, H_2'), 6.09 (1H, s, H_4'), 6.17 (1H, d, J= 16.0 Hz, H_1'). ^{13}C NMR (75 MHz, C_6D_6): δ 19.8 (t, C_5), 20.2 (q), 22.0 (q), 29.2 (q, 2x), 33.3 (t, C_6), 34.5 (s, C_3), 39.9 (t, C_4), 83.0 (d, C_4'), 128.3 (s), 129.7 (d), 134.7 (d), 137.8 (s), 145.8 (s). Data for **19**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (6H, s, C_3-2CH_3), 1.4-1.6 (4H, m, $2H_4$ and $2H_5$), 1.69 (3H, s, C_1-CH_3), 1.8-2.0 (2H, m, $2H_6$), 1.98 (3H, d, J= 2.2 Hz, C_4'-CH_3), 5.40 (1H, dd, J= 16.3, 2.2 Hz, H_2'), 6.47 (1H, d, J= 16.3 Hz, H_1'). ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.6 (q), 19.4 (t), 21.8 (q), 29.0 (q, 2x), 33.2 (t), 34.2 (s), 39.7 (t), 79.4 (s), 85.9 (s), 112.8 (d), 130.9 (s), 137.3 (s), 139.8 (d).

General procedure for the palladium-catalyzed coupling reactions. Separate solutions of the boronic acid in THF (~ 10^{-3} M), the alkenyliodide and the catalyst in THF (~ 10^{-3} M), and 10% aq. TlOH were individually degassed by bubbling argon through the solutions for 15 min. The base was added to the boronic acid and the resulting solution was stirred for 5 min. The solution containing alkenyliodide and the catalyst was then added via cannula and stirring was maintained at rt for the indicated length of time (Table

1). The mixture was diluted with ether, filtered through Celite, and the filtrate was washed with $NaHCO_3$. The aqueous layer was then extracted with ether and the combined extracts were dried over $MgSO_4$ and concentrated. The crude product was purified first by chromatography on silica gel (80:20 hexane/ethyl acetate for the retinols; 99:1 hexane/pyridine for the retinyl silyl ethers), and then by HPLC (μPorasil, 83:17 hexane/ethyl acetate, 2 mL/min for the retinols; hexane, 2 mL/min for the retinyl silyl ethers) to afford the pure retinoids as colorless-to-yellow oils.

Table 1. Reaction conditions and yields for the Suzuki coupling reactions.

Entry	Boronic Acid (mmol)	Iodide (mmol)	$Pd(PPh_3)_4$ (mmol)	10% aq. TlOH (mmol)	Reaction Time (h)	Product	Yield (%)
1	**10**[13c] (0.06)	**18** (0.05)	0.005	0.19	0.5	**1**	83
2	**12**[9b,c] (0.75)	**14** (0.60)	0.064	2.31	0.5	**7**	50
3	**12**[9b,c] (0.45)	**17** (0.32)	0.040	1.35	0.5	**8**	40
4	**16** (0.31)	**18** (0.23)	0.030	0.90	18	**9**	60
5	**12**[9b,c] (0.54)	**26** (0.43)	0.046	1.66	0.5	**28**	63
6	**32**[9c] (1.13)	**26** (0.90)	0.100	3.50	0.5	**33**	58
7	**32**[9c] (0.46)	**14** (0.37)	0.040	1.42	0.5	**36**	51
8	**10**[13c] (0.61)	**45** (0.30)	0.030	1.85	12	**46**	70

Retinol (1). Table 1. Spectral data matched those reported[11a] for vitamin A.

9-Demethylretinol (7) and 2-[(*E*,*E*)-buta-1',3'-dien-1'-yl]-1,3,3-trimethylcyclohexene (20). Table 1. Triene **20** (10% yield) was also obtained. Data for **7**: ^1H NMR (250 MHz, $CDCl_3$): δ 1.02 (6H, s, C_1-$2CH_3$), 1.4-1.7 (4H, m, $2H_2$ and $2H_3$), 1.72 (3H, s, C_5-CH_3), 1.83 (3H, s, C_{13}-CH_3), 2.02 (2H, t, J= 6.1 Hz, $2H_4$), 4.30 (2H, d, J= 6.9 Hz, $2H_{15}$), 5.67 (1H, t, J= 6.9 Hz, H_{14}), 6.1-6.3 (6H, m, H_7, H_8, H_9, H_{10}, H_{11} and H_{12}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 12.4 (q), 19.1 (t), 21.6 (q), 28.8 (q, 2x), 33.2 (t), 34.1 (s), 39.7 (t), 59.5 (t), 129.2 (s), 130.0 (d), 130.4 (d), 131.2 (d), 132.0 (d), 133.3 (d), 134.4 (d), 135.9 (d), 136.8 (s), 137.5 (s). IR ($CHCl_3$): υ 3600-3200 (br, H-bonded O-H), 3080 (m, C-H), 2930 (w, C-H), 1580 (m), 1250 (m), 950 (s) cm^{-1}. UV (EtOH): λ_{max} (ε) 308 (27900), 318 (32300), 352 (sh) nm. MS m/z (%): 272 (M^+, 7), 241 (7), 205 (3), 171 (15), 147 (59), 109 (65), 105 (89), 91 (100), 69 (95), 55 (96). HRMS: Calcd. for $C_{19}H_{28}O$: 272.2140. Found: 272.2142. Data for **20**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (6H, s, C_3-$2CH_3$), 1.4-1.6 (4H, m, $2H_4$ and $2H_5$), 1.70 (3H, s, C_1-CH_3), 2.00 (2H, t, J= 6.2 Hz, $2H_6$), 5.01 (1H, dd, J= 10.0, 1.6 Hz, $H_{4'trans}$), 5.13 (1H, dd, J= 16.9, 1.6 Hz, $H_{4'cis}$), 6.04 (1H, dd, J= 15.8, 10.0 Hz, $H_{2'}$), 6.15 (1H, d, J= 15.8 Hz, $H_{1'}$), 6.40 (1H, dt, J= 16.9, 10.0 Hz, $H_{3'}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5 (t, C_5), 21.9 (q, C_1-CH_3), 29.1 (q, 2x), 33.3 (t, C_6), 34.3 (s, C_3), 39.8 (t, C_4), 115.2 (t, $C_{4'}$), 130.0 (s), 132.2 (d), 134.1 (d), 137.4 (s), 138.2 (d). MS m/z (%): 176 (M^+, 27), 175 (17), 161 (36), 147 (34), 133 (42), 119 (71), 105 (100), 91 (90), 69 (56), 57 (61).

9,13-bis-Demethylretinol (8). Table 1. ^1H NMR (250 MHz, $CDCl_3$): δ 1.03 (6H, s, C_1-$2CH_3$), 1.4-1.7 (4H, m, $2H_2$ and $2H_3$), 1.72 (3H, s, C_5-CH_3), 2.04 (2H, t, J= 6.1 Hz, $2H_4$), 4.20 (2H, t, J= 5.8 Hz, $2H_{15}$), 5.84 (1H, dt, J= 14.9, 5.8 Hz, H_{14}), 6.0-6.4 (7H, m, H_7-H_{13}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 19.1 (t), 21.6 (q), 28.8 (q, 2x), 33.2 (t), 34.1 (s, C_1), 39.7 (t, C_4), 63.5 (t, C_{15}), 130.5 (s), 130.8 (d), 131.1 (d), 131.6 (d), 132.0 (d), 132.4 (d), 133.2 (d), 133.7 (d), 134.7 (d), 137.5 (s). IR ($CHCl_3$): υ 3600-3200 (br, H-bonded OH), 3030 (s, C-H), 2930 (s, C-H), 2870 (s, C-H), 1460 (m), 1230 (w) cm^{-1}. UV (MeOH): λ_{max} (ε) 318 (40500),

350 (sh) nm. MS m/z (%): 258 (M^+, 100), 243 (41), 227 (35), 171 (25), 159 (47), 147 (47), 145 (50), 143 (42), 131 (51), 129 (48), 119 (36), 117 (36), 105 (70), 91 (89), 79 (52), 77 (43). HRMS: Calcd. for $C_{20}H_{30}O$: 258.1983. Found: 258.1979.

13-Demethylretinol (9). Table 1. ^1H NMR (250 MHz, $CDCl_3$) : δ 1.02 (6H, s, C_1-$2CH_3$), 1.4-1.7 (4H, m, $2H_2$ and $2H_3$), 1.72 (3H, s, C_5-CH_3), 1.95 (3H, s, C_9-CH_3), 1.9-2.1 (2H, m, $2H_4$), 4.22 (2H, d, J= 6.0 Hz, $2H_{15}$), 5.85 (1H, dt, J= 14.5, 6.0 Hz, H_{14}), 6.07 (1H, d, J= 11.3 Hz, H_{10}), 6.09 (1H, d, J= 16.2 Hz, H_8), 6.19 (1H, d, J= 16.2 Hz, H_7), 6.25 (1H, dd, J= 14.2, 10.8 Hz, H_{12}), 6.37 (1H, dd, J= 14.5, 10.8 Hz, H_{13}), 6.60 (1H, dd, J= 14.2, 11.3 Hz, H_{11}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 12.6 (q), 19.2 (t), 21.7 (q), 28.9 (q, 2x), 33.0 (t), 34.2 (s), 39.6 (t), 63.5 (t), 127.2 (d), 129.1 (s), 129.4 (s), 129.6 (d), 130.0 (d), 131.4 (d), 131.5 (d), 132.3 (d), 137.5 (d), 137.9 (s). UV (MeOH): λ_{max} (ε) 322 (36000) nm. HRMS: Calcd. for $C_{19}H_{28}O$: 272.2140. Found: 272.2129.

(11*Z*)-9-Demethylretinyl-*tert*-Butyldimethylsilyl Ether (28). Table 1. ^1H NMR (250 MHz, $CDCl_3$): δ 0.09 (6H, s, Si-$2CH_3$), 0.92 (9H, s, Si-*t*-Bu), 1.03 (6H, s, C_1-$2CH_3$), 1.4-1.7 (4H, m, $2H_2$ and $2H_3$), 1.74 (3H, s, C_5-CH_3), 1.86 (3H, s, C_{13}-CH_3), 2.00 (2H, t, J= 6.2 Hz, $2H_4$), 4.33 (2H, d, J= 6.2 Hz, $2H_{15}$), 5.62 (1H, t, J= 6.2 Hz, H_{14}), 5.81 (1H, d, J= 11.7 Hz, H_{12}), 6.05 (1H, t, J= 11.7 Hz, H_{11}), 6.2-6.4 (3H, m, H_7, H_8 and H_9), 6.75 (1H, dd, J= 14.6, 11.7 Hz, H_{10}). MS m/z (%): 386 (M^+, 59), 371 (6), 322 (26), 254 (13), 249 (15), 242 (11), 241 (52), 239 (40), 210 (100), 147 (37), 131 (30), 105 (51), 93 (33), 91 (44), 75 (85), 73 (96). HRMS: Calcd. for $C_{25}H_{42}OSi$: 386.3005. Found: 386.2994.

(11*Z*)-9-Demethylretinol (29). To a solution of silyl ether **28** (64 mg, 0.16 mmol) in THF (3 mL) was added TBAF (0.30 mL, 1.1 M in THF, 0.33 mmol) and the mixture was stirred at rt for 4 h. After dilution with ether, the mixture was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (80:20 hexane/ethyl acetate) to afford 32 mg (71%) of compound **29**. ^1H NMR (250 MHz, $CDCl_3$): δ 1.03 (6H, s, C_1-$2CH_3$), 1.4-1.7 (4H, m, $2H_2$ and $2H_3$), 1.72 (3H, s, C_5-CH_3), 1.90 (3H, s, C_{13}-CH_3), 2.01 (2H, t, J= 6.1 Hz, $2H_4$), 4.28 (2H, d, J= 6.7 Hz, $2H_{15}$), 5.70 (1H, t, J= 6.7 Hz, H_{14}), 5.81 (1H, d, J= 11.7 Hz, H_{12}), 6.02 (1H, t, J= 11.7 Hz, H_{11}), 6.1-6.4 (3H, m, H_7, H_8 and H_9), 6.71 (1H, dd, J= 14.3, 11.7 Hz, H_{10}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 16.9 (q), 19.2 (t), 21.7 (q), 28.8 (q, 2x), 33.2 (t), 34.1 (s), 39.7 (t), 59.5 (t), 127.7 (d), 129.2 (s), 129.5 (d), 130.0 (d), 132.2 (d), 132.6 (d), 133.3 (d), 136.1 (d), 136.6 (s), 137.5 (s). UV (MeOH): λ_{max} (ε) 320 (39500) nm. MS m/z (%): 272 (M^+, 20), 241 (17), 199 (13), 171 (29), 149 (75), 111 (100), 91 (76), 69 (50), 55 (47). HRMS: Calcd. for $C_{19}H_{28}O$: 272.2140. Found: 272.2141.

(11*Z*)-9-Demethylretinal (30). To a solution of (11Z)-9-demethylretinol **29** (9 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added MnO_2 (86 mg, 0.99 mmol) in one portion at rt. The suspension was stirred at rt for 1 h, filtered through Celite and concentrated. The residue was purified by chromatography on silica gel (95:5 hexane/ethyl acetate) to afford 8 mg (89%) of compound **30**. An analytical sample was obtained after HPLC purification (92:8 hexane/ethyl acetate, 2 mL/min). ^1H NMR data matched that reported[25d,34] for this compound. MS m/z (%): 270 (M^+, 31), 227 (3), 205 (7), 173 (13), 159 (37), 105 (58), 91 (100), 77 (53), 55 (23). HRMS: Calcd. for $C_{19}H_{26}O$: 270.1985. Found: 270.1985.

9-Demethylretinal (31). Following the procedure described above, compound **31** was obtained in 90% yield. ^{1}H NMR data matched those reported[25d,34] for this compound. IR ($CHCl_3$): υ 3125 (m, C-H), 3030 (m, C-H), 2920 (m, C-H), 2830 (m, C-H), 1655 (s, C=O), 1560 (m), 1000 (m) cm^{-1}. UV (EtOH): λ_{max} (ε) 374 (42700) nm (lit.[25b,c]: λ_{max} 373 nm). MS m/z (%): 270 (M^+, 25), 173 (18), 159 (55), 147 (54), 145 (43), 131 (44), 128 (36), 119 (54), 115 (48), 105 (88), 91 (100), 81 (52), 77 (78), 69 (50), 55 (57). HRMS: Calcd. for $C_{19}H_{26}O$: 270.1985. Found: 270.1981.

(11Z)-9-Demethyl-7,8-dihydroretinyl-*tert*-Butyldimethylsilyl Ether (33). Table 1. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.08 (6H, s, Si-$2CH_3$), 0.91 (9H, s, Si-*t*-Bu), 0.99 (6H, s, C_1-$2CH_3$), 1.4-1.6 (4H, m, $2H_2$ and $2H_3$), 1.59 (3H, s, C_5-CH_3), 1.83 (3H, s, C_{13}-CH_3), 1.91 (2H, t, J= 6.1 Hz, $2H_4$), 2.0-2.2 (4H, m, $2H_7$ and $2H_8$), 4.31 (2H, d, J= 6.1 Hz, $2H_{15}$), 5.58 (1H, t, J= 6.1 Hz, H_{14}), 5.71 (1H, d, J= 11.4 Hz, H_{12}), 5.72 (1H, dt, J= 14.6, 6.5 Hz, H_9), 5.94 (1H, t, J= 11.4 Hz, H_{11}), 6.59 (1H, dd, J= 14.6, 11.4 Hz, H_{10}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 (q), 17.3 (s, Si-C), 18.5 (t), 18.9 (q), 24.9 (q, Si-*t*-Bu), 27.4 (t), 27.6 (q, C_1-$2CH_3$), 31.7 (t), 32.7 (t), 33.8 (s, C_1), 38.8 (t), 59.3 (t), 125.6 (d), 126.2 (s), 127.8 (d), 129.8 (d), 130.1 (d), 132.8 (s), 135.7 (d), 135.8 (s). IR ($CHCl_3$): υ 2960 (s, C-H), 2930 (s, C-H), 2860 (m, C-H), 1475 (m), 1260 (m), 1100 (w), 1050 (m), 840 (s) cm^{-1}. MS m/z (%): 388 (M^+, 1), 331 (12), 251 (9), 193 (9), 167 (49), 137 (58), 105 (27), 95 (60), 75 (100). HRMS: Calcd. for $C_{25}H_{44}OSi$: 388.3163. Found: 388.3168.

(11Z)-9-Demethyl-7,8-dihydroretinol (34). Following the procedure described for **29**, compound **34** was obtained in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (6H, s, C_1-$2CH_3$), 1.4-1.6 (4H, m, $2H_2$ and $2H_3$), 1.59 (3H, s, C_5-CH_3), 1.89 (3H, s, C_{13}-CH_3), 1.90 (2H, t, J= 6.2 Hz, $2H_4$), 2.0-2.2 (4H, m, $2H_7$ and $2H_8$), 4.28 (2H, t, J= 6.4 Hz, $2H_{15}$), 5.67 (1H, t, J= 6.4 Hz, H_{14}), 5.72 (1H, d, J= 11.6 Hz, H_{12}), 5.75 (1H, dt, J= 14.9, 7.2 Hz, H_9), 5.96 (1H, t, J= 11.6 Hz, H_{11}), 6.57 (1H, dd, J= 14.9, 11.6 Hz, H_{10}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3 (q), 19.8 (t), 20.2 (q), 28.6 (t), 28.8 (q, 2x), 33.0 (t), 34.0 (t), 35.1 (s), 40.0 (t), 59.6 (t), 126.7 (d), 127.6 (s), 129.7 (d), 129.8 (d), 131.0 (d), 136.6 (s), 137.0 (s), 137.7 (d). UV (EtOH): λ_{max} (ε) 272 (27000) nm. MS m/z (%): 274 (M^+, 5), 163 (10), 137 (100), 95 (92), 81 (57). HRMS: Calcd. for $C_{19}H_{30}O$: 274.2298. Found: 274.2298.

9-Demethyl-7,8-dihydroretinol (36). Table 1. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.99 (6H, s, C_1-$2CH_3$), 1.3-1.6 (4H, m, $2H_2$ and $2H_3$), 1.60 (3H, s, C_5-CH_3), 1.81 (3H, s, C_{13}-CH_3), 1.91 (2H, t, J= 6.1 Hz, $2H_4$), 2.0-2.2 (4H, m, $2H_7$ and $2H_8$), 4.29 (2H, d, J= 7.0 Hz, $2H_{15}$), 5.64 (1H, t, J= 7.0 Hz, H_{14}), 5.78 (1H, dt, J= 15.0, 6.3 Hz, H_9), 6.1-6.2 (3H, m, H_{10}, H_{11} and H_{12}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7 (q), 19.8 (t), 20.1 (q), 28.7 (t), 28.8 (q, 2x), 33.0 (t), 33.9 (t), 35.1 (s), 40.0 (t), 59.6 (t), 127.6 (s), 129.2 (d), 129.7 (d), 130.3 (d), 134.7 (d), 135.8 (d), 136.7 (s), 137.0 (s). IR ($CHCl_3$): υ 3610 (w, O-H), 3600-3300 (w, br, O-H), 3010 (w, C-H), 2930 (s, C-H), 2870 (m, C-H), 970 (m) cm^{-1}. UV (EtOH): λ_{max} (ε) 270 (22900) nm. MS m/z (%): 274 (M^+, 8), 137 (100), 110 (25), 109 (42), 95 (99), 81 (65). HRMS: Calcd. for $C_{19}H_{30}O$: 274.2298. Found: 274.2295.

(11Z)-9-Demethyl-7,8-dihydroretinal (35). Obtained in 91% yield according to the procedure described for **30**. Yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.92 (6H, s, C_1-$2CH_3$), 1.2-1.4 (4H, m, $2H_2$ and $2H_3$),

1.52 (3H, s, C_5-CH_3), 1.8-2.2 (6H, m, $2H_4$, $2H_7$ and $2H_8$), 2.27 (3H, s, C_{13}-CH_3), 5.73 (1H, d, J= 11.5 Hz, H_{12}), 5.9-6.0 (2H, m, H_9 and H_{14}), 6.19 (1H, t, J= 11.5 Hz, H_{11}), 6.51 (1H, dd, J= 14.6, 11.5 Hz, H_{10}), 10.00 (1H, d, J= 8.2 Hz, H_{15}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 17.7 (q), 19.4 (t, C_3), 19.8 (q), 28.0 (t), 28.5 (q, 2x), 32.6 (t), 33.8 (t, C_4), 34.8 (s, C_1), 39.7 (t, C_2), 126.2 (d), 127.7 (s, C_5), 129.0 (d), 129.6 (d), 135.8 (d), 136.5 (s, C_6), 142.3 (d), 155.9 (s, C_{13}), 191.3 (d, C_{15}). IR ($CHCl_3$): υ 3030 (s, C-H), 2960 (m, C-H), 1675 (s, C=O), 1225 (m) cm^{-1}. UV (EtOH): λ_{max} (ε) 298 (11900), 322 (14600) nm. MS m/z (%): 257 (M^+-15, 3), 241 (6), 137 (20), 135 (23), 129 (39), 123 (40), 95 (76), 81 (70), 69 (88), 57 (100). HRMS: Calcd. for $C_{19}H_{28}O$: 272.2141. Found: 272.2132.

9-Demethyl-7,8-dihydroretinal (37). Following the procedure described for **30**, compound **37** was obtained in 81% yield. Yellow crystals (m.p. 49-51 °C, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (6H, s, C_1-$2CH_3$), 1.4-1.6 (4H, m, $2H_2$ and $2H_3$), 1.60 (3H, s, C_5-CH_3), 1.91 (2H, t, J= 6.2 Hz, $2H_4$), 2.0-2.2 (4H, m, $2H_7$ and $2H_8$), 2.27 (3H, d, J= 0.9 Hz, C_{13}-CH_3), 5.94 (1H, d, J= 8.2 Hz, H_{14}), 6.0-6.1 (1H, m, H_9), 6.21 (1H, dd, J= 15.3, 10.3 Hz, H_{10}), 6.27 (1H, d, J= 15.3 Hz, H_{12}), 6.73 (1H, dd, J= 15.3, 10.3 Hz, H_{11}), 10.10 (1H, d, J= 8.2 Hz, H_{15}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.2 (q), 19.7 (t), 20.2 (q), 28.3 (t), 28.8 (q, 2x), 33.0 (t), 34.1 (t), 35.2 (s), 40.0 (t), 127.9 (s), 129.3 (d), 129.8 (d), 133.3 (d), 136.7 (s), 137.0 (d), 141.5 (d), 155.1 (s), 191.5 (d, C_{15}). IR ($CHCl_3$): υ 3020 (m, C-H), 2930 (m, C-H), 1650 (s, C=O), 1630 (m), 1590 (s, C=C), 980 (m) cm^{-1}. UV (EtOH): λ_{max} (ε) 324 (39900) nm. MS m/z (%): 272 (M^+, 8), 137 (61), 136 (44), 107 (24), 121 (26), 95 (100), 81 (67). HRMS: Calcd. for $C_{19}H_{28}O$: 272.2141. Found: 272.2144.

(1*R*,6*S*)-2,2,6-Trimethylcyclohexane-1-carbaldehyde (40). A solution of acetate **39**[26] (3.0 g, 0.015 mol) in toluene (6 mL) was added to 85% H_3PO_4 (6.0 g, 0.061 mol) and the mixture was heated to 100 °C for 12 h. After cooling to rt, the mixture was poured into H_2O and extracted with toluene (3 x 30 mL). The organic layer was washed with saturated aq. $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated. Distillation of the residue (b.p. 63 °C/5.5 mm Hg; bibl.[26] 74-76 °C/14 mm Hg) afforded compound **40** (1.18 g, 50%; 90:10 *trans/cis*) as a colorless oil. Data for the *trans* isomer: ^1H NMR (250 MHz, $CDCl_3$): δ 0.80 (3H, d, J= 6.4 Hz, C_6-CH_3), 0.95 (1H, m, H_6), 0.98 and 1.03 (6H, 2s, C_2-$2CH_3$), 1.2-1.4 (4H, m), 1.63 (1H, dd, J= 12.1 Hz, 5.0 Hz, H_1), 1.8-2.0 (2H, m), 9.64 (1H, d, J= 5.0 Hz, CHO). ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.6 (q, 2x), 20.8 (t), 27.6 (q), 30.8 (d), 33.7 (s), 34.2 (t), 41.4 (t), 66.1 (d), 207.2 (d). IR ($CHCl_3$): υ 3010 (s, C-H), 2960 (s, C-H), 2925 (s, C-H), 1710 (s, C=O), 1215 (s) cm^{-1}. MS m/z (%): 153 (M^+-1, 38), 125 (99), 110 (74), 109 (57), 69 (100), 55 (65).

Ethyl (*E*)-3-[(1'*S*,6'*S*)-(2',2',6'-Trimethylcyclohex-1'-yl)]prop-2-enoate (41). To a vigorously stirred solution of triethyl phosphonoacetate (1.59 mL, 7.93 mmol) in DMF (6 mL) at 0 °C was added NaOEt (567 mg, 8.33 mmol) followed by a solution of aldehyde **40** (1.12 g, 7.29 mmol) in DMF (4 mL) dropwise. After stirring at rt for 12 h, ether and H_2O were added, the layers were separated and the organic layer was washed with brine. The aqueous layer was then extracted with ether (3 x 50 mL), the combined organic layers were dried over $MgSO_4$ and evaporated. Distillation (115 °C/5 mm Hg) afforded 1.10 g (67%) of compound **41** (90:10 *trans/cis*) as a colorless oil. Data for the *trans* isomer: ^1H NMR (250 MHz, $CDCl_3$): δ 0.73 (3H, d, J= 5.6 Hz, $C_{6'}$-CH_3), 0.80 and 0.86 (6H, 2s, $C_{2'}$-$2CH_3$), 1.27 (3H, t, J= 7.1 Hz, -$OCH_2\underline{CH_3}$), 1.0-1.8 (8H, m, $2H_{3'}$, $2H_{4'}$, $2H_{5'}$, $H_{1'}$, $H_{6'}$), 4.17 (2H, q, J= 7.1 Hz, -$O\underline{CH_2}CH_3$), 5.74 (1H, d, J= 15.5 Hz, H_2), 6.72 (1H, dd, J= 15.5, 10.2 Hz, H_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.1 (q),

20.3 (q), 21.4 (q), 21.7 (t), 31.2 (q), 31.3 (d), 33.7 (s), 35.1 (t), 41.2 (t), 58.2 (d), 60.0 (t), 123.0 (d), 150.9 (d), 166.4 (s). IR ($CHCl_3$): υ 2960 (s, C-H), 2930 (s, C-H), 2870 (m, C-H), 1710 (s, C=O), 1650 (m), 1460 (m), 1440 (m), 1255 (m), 1185 (m) cm^{-1}. MS m/z (%): 179 ($M\text{-}OEt^+$, 12), 167 (13), 151 (8), 139 (19), 136 (59), 125 (34), 111 (38), 109 (49), 107 (28), 95 (90), 94 (25), 93 (38), 81 (72), 69 (97), 55 (100). HRMS: Calcd. for $C_{14}H_{24}O_2$: 224.1776. Found: 224.1778.

(*E*)-3-[(1'*S*,6'*S*)-(2',2',6'-Trimethylcyclohex-1'-yl)]prop-2-en-1-ol (42). A solution of ester **41** (3.52 g, 15.72 mmol) in ether (14 mL) was added via cannula to a suspension of $LiAlH_4$ (0.71 g, 18.71 mmol) in ether (40 mL) at 0 °C. After stirring for 5 h at 0 °C, water was added, and the layers were separated. The aqueous layer was saturated with NaCl and extracted with ether (5 x 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. Distillation of the residue (60 °C/0.5 mm Hg) afforded 2.8 g (98%) of compound **42** (90:10 *trans/cis*) as a colorless oil. Data for the *trans* isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 0.64 (3H, d, J= 6.1 Hz, $C_{6'}\text{-}CH_3$), 0.70 (6H, s, $C_{2'}\text{-}2CH_3$), 1.1-1.7 (8H, m, $H_{1'}$, $2H_{3'}$, $2H_{4'}$, $2H_{5'}$ and $H_{6'}$), 3.99 (2H, d, J= 5.8 Hz, $2H_1$), 5.26 (1H, dd, J= 15.3, 9.3 Hz, H_3), 5.44 (1H, dt, J= 15.3, 5.8 Hz, H_2). ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.3 (q), 21.5 (q), 21.9 (t), 31.3 (q), 31.4 (d), 33.4 (s), 35.5 (t), 41.4 (t), 58.0 (d), 63.8 (t), 131.0 (d), 134.0 (d). IR ($CHCl_3$): υ 3610 (m, O-H), 2950 (s, C-H), 2925 (s, C-H), 2870 (s, C-H) cm^{-1}. MS m/z (%): 165 ($M^+\text{-}OH$, 11), 149 (33), 121 (18), 105 (33), 95 (49), 79 (52), 77 (48), 69 (71), 55 (100). HRMS: Calcd. for $C_{12}H_{22}O$: 182.1672. Found: 182.1677.

(*E*)-3-[(1'*S*,6'*S*)-(2',2',6'-Trimethylcyclohex-1'-yl)]prop-2-enal (43). According to the general procedure described for **30**, treatment of alcohol **42** (0.72 g, 3.96 mmol) in CH_2Cl_2 (30 mL) with MnO_2 (3.78 g, 43.50 mmol) at rt for 12 h afforded, after chromatography (SiO_2, 90:10 hexane/ether) 0.58 g (81%) of compound **43**. $[\alpha]_D^{20}$= + 36° (c= 1.4, EtOH). ^1H NMR (250 MHz, $CDCl_3$): δ 0.75 (3H, d, J= 6.1 Hz, $C_{6'}\text{-}CH_3$), 0.83 and 0.90 (6H, 2s, $C_{2'}\text{-}2CH_3$), 1.4-1.8 (8H, m, $H_{1'}$, $2H_{3'}$, $2H_{4'}$, $2H_{5'}$ and $H_{6'}$), 6.08 (1H, dd, J= 15.5, 8.0 Hz, H_2), 6.62 (1H, dd, J= 15.5, 10.0 Hz, H_3), 9.51 (1H, d, J= 8.0 Hz, H_1). ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.4 (q), 21.3 (q), 21.7 (t), 31.2 (q), 31.3 (d), 34.0 (s), 35.0 (t), 41.1 (t), 58.7 (d), 135.1 (d), 160.6 (d), 193.8 (d, C_1). IR ($CHCl_3$): υ 2970 (s, C-H), 2940 (s, C-H), 2880 (m, C-H), 1690 (s, C=O) cm^{-1}. MS m/z (%): 180 (M^+, 7), 165 (8), 95 (63), 81 (51), 69 (42), 55 (36), 41 (48), 32 (100). HRMS: Calcd. for $C_{12}H_{20}O$: 180.1515. Found: 180.1513.

(2*S*,3*S*)-2-[(*E*)-But-1'-en-3'-yn-1'-yl]-1,1,3-trimethylcyclohexane (44). KO*t*-Bu (1.06 g, 9.45 mmol) was added to a suspension of iodomethyltriphenylphosphonium iodide (2.51 g, 4.74 mmol) in THF (90 mL) at rt. The resulting solution was cooled to -78 °C, and then a solution of aldehyde **43** (0.85 g, 4.74 mmol) in THF (10 mL) was added. After stirring at -78 °C for 2 h, the solution was allowed to reach room temperature, diluted with hexane and washed with brine and water. The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. Chromatography (SiO_2, 90:10 hexane/ether) afforded 0.73 g (88%) of compound **44**. ^1H NMR (250 MHz, $CDCl_3$): δ 0.77 (3H, d, J= 5.9 Hz, $C_3\text{-}CH_3$), 0.83 and 0.85 (6H, 2s, $C_1\text{-}2CH_3$), 1.1-1.8 (8H, m, H_2, H_3, $2H_4$, $2H_5$ and $2H_6$), 2.78 (1H, d, J= 2.1 Hz, $H_{4'}$), 5.39 (1H, dd, J= 16.0, 2.1 Hz, $H_{2'}$), 6.00 (1H, dd, J= 16.0, 9.6 Hz, $H_{1'}$). ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.3 (q), 21.4 (q), 21.8 (t), 31.3 (q), 31.4 (d), 33.7 (s), 35.4 (t), 41.3 (t), 59.2 (d), 75.1 (s), 82.7 (d), 110.0 (d), 148.3 (d). HRMS: Calcd. for $C_{13}H_{20}$: 176.1565. Found: 176.1564.

(2*S*,3*S*)-2-[(*E*,*E*)-4'-Iodobuta-1',3'-dien-1'-yl]-1,1,3-trimethylcyclohexane (45). Anhydrous $CrCl_2$ (0.43 g, 3.49 mmol) was suspended in THF (4 mL) under argon. A solution of aldehyde **43** (0.10 g, 0.55 mmol) and iodoform (0.45 g, 1.13 mmol) in THF (4 mL) was then added dropwise to the suspension at 0 °C. After stirring at rt for 3 h, the reaction mixture was poured into water and extracted with ether (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and evaporated. Chromatography (SiO_2, hexane) afforded 150 mg (89%) of compound **45**, as a 4:1 mixture of 1*E*/1*Z* stereoisomers, as determined by ^1H NMR. The mixture of isomers was treated with a solution of NaOH (1 mg, 0.24 mmol) in n-butanol (0.33 mL). The resulting solution was heated to reflux for 5 h. After cooling to rt, it was diluted with ether and washed with brine. The aqueous layer was extracted with ether (3 x 10 mL), the combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by passing through a short chromatography column (SiO_2, hexane) to afford 60 mg (60%) of pure (*E*)-iodide **45**. $[\alpha]_D^{20}$= + 21° (c= 0.06, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 0.74 (3H, d, J= 6.2 Hz, C_3-CH_3), 0.80 and 0.82 (6H, 2s, C_1-$2CH_3$), 1.1-1.7 (8H, m, H_2, H_3, $2H_4$, $2H_5$ and $2H_6$), 5.45 (1H, dd, J= 15.1, 9.8 Hz, $H_{1'}$), 5.90 (1H, dd, J= 15.1, 10.6 Hz, $H_{2'}$), 6.15 (1H, d, J= 14.4 Hz, $H_{4'}$), 7.01 (1H, dd, J= 14.4, 10.6 Hz, $H_{3'}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7 (q), 21.9 (q), 22.2 (t), 31.7 (q), 31.8 (d), 34.0 (s), 35.7 (t), 41.6 (t), 58.7 (d), 76.3 (d), 132.1 (d), 138.1 (d), 145.8 (d). MS m/z (%): 304 (M^+, 7), 106 (34), 91 (34), 69 (37), 32 (100). HRMS: Calcd. for $C_{13}H_{21}I$: 304.0689. Found: 304.0692.

(5*S*,6*S*)-9-Demethyl-5,6-dihydroretinol (46). Table 1. $[\alpha]_D^{20}$= + 40.5° (c= 0.1, EtOH). ^1H NMR (250 MHz, $CDCl_3$): δ 0.74 (3H, d, J= 5.9 Hz, C_5-CH_3), 0.80 and 0.81 (6H, 2s, C_1-$2CH_3$), 1.1-1.7 (8H, m, $2H_2$, $2H_3$, $2H_4$, H_5 and H_6), 1.80 (3H, s, C_{13}-CH_3), 4.28 (2H, d, J= 7.0 Hz, $2H_{15}$), 5.45 (1H, dd, J= 14.8, 9.2 Hz, H_9), 5.65 (1H, t, J= 7.0 Hz, H_{14}), 6.01 (1H, dd, J= 15.0, 10.0 Hz, H_{11}), 6.1-6.3 (4H, m, H_7, H_8, H_{10} and H_{12}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 12.4 (q), 20.4 (q), 21.6 (q), 21.9 (t), 31.4 (q), 31.8 (d), 33.9 (s), 35.5 (t), 41.4 (t), 58.7 (d), 59.4 (t), 129.1 (d), 129.8 (d), 130.5 (d), 132.3 (d), 133.6 (d), 135.7 (d), 136.7 (s), 137.3 (d). IR ($CHCl_3$): υ 3600-3200 (br, H-bonded O-H), 3060 (w, C-H), 2920 (s, C-H), 2870 (m, C-H), 1450 (m), 1000 (m) cm^{-1}. UV (EtOH): λ_{max} (ε) 282 (sh), 290 (24900), 302 (35000), 318 (30700) nm. MS m/z (%): 274 (M^+, 11), 261 (18), 247 (17), 165 (23), 149 (29), 137 (40), 135 (35), 133 (27), 123 (68), 119 (60), 109 (98), 95 (100), 91 (75), 81 (93), 69 (90), 55 (69). HRMS: Calcd. for $C_{19}H_{30}O$: 274.2298. Found: 274.2290.

(5*S*,6*S*)-9-Demethyl-5,6-dihydroretinal (47). Following the general oxidation procedure described for **30**, compound **47** was obtained in 99% yield. Yellow oil. $[\alpha]_D^{20}$= + 43° (c= 0.03, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 0.76 (3H, d, J= 5.9 Hz, C_5-CH_3), 0.82 and 0.84 (6H, 2s, C_1-$2CH_3$), 1.2-1.8 (8H, m, $2H_2$, $2H_3$, $2H_4$, H_5 and H_6), 2.28 (3H, d, J= 1.0 Hz, C_{13}-CH_3), 5.63 (1H, dd, J= 15.0, 9.4 Hz, H_7), 5.95 (1H, d, J= 8.1 Hz, H_{14}), 6.08 (1H, dd, J= 15.0, 10.6 Hz, H_8), 6.25 (1H, dd, J= 15.0, 10.6 Hz, H_{10}), 6.33 (1H, d, J= 15.0 Hz, H_{12}), 6.47 (1H, dd, J= 15.0, 10.6 Hz, H_9), 6.78 (1H, dd, J= 15.0, 10.6 Hz, H_{11}), 10.1 (1H, d, J= 8.1 Hz, H_{15}). ^{13}C NMR (63 MHz, $CDCl_3$): δ 12.9 (q), 20.4 (q), 21.6 (q), 21.9 (t), 31.5 (q), 31.8 (d), 34.0 (s), 35.4 (t), 41.4 (t), 59.0 (d), 129.1 (d), 129.6 (d), 132.1 (d), 134.1 (d), 136.8 (d), 138.3 (d), 141.0 (d), 154.6 (s), 191.2 (d). UV (EtOH): λ_{max} (ε) 360 (39800) nm. MS m/z (%): 272 (M^+, 73), 245 (14), 197 (9), 161 (21), 147 (49), 133 (100), 109 (88), 91 (69), 69 (36). HRMS: Calcd. for $C_{19}H_{28}O$: 272.2141. Found: 272.2148.

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REFERENCES AND NOTES

1. (a) Sporn, M. B.; Roberts, A. B.; Goodman, D. S. Eds. *The Retinoids*; Academic Press: New York, 1984; vol 1 & 2. (b) Sporn, M. B.; Roberts, A. B.; Goodman, D. S. Eds. *The Retinoids: Biology, Chemistry and Medicine*, 2nd ed.; Raven: New York, 1993. (c) Saurat, J. H. Ed. *Retinoids: New Trends in Research and Therapy*; S. Karger: Basel, 1985. (d) Sherman, M. I. Ed. *Retinoids and Cell Differentiation*; CRC Press: Boca Raton, FL, 1986. (e) Dawson, M. I.; Okamura, W. H. Eds. *Chemistry and Biology of Synthetic Retinoids*; CRC Press: Boca Raton, FL, 1990. (f) Packer, L. Ed. *Methods in Enzymology* vol 89, Retinoids Part A; Academic Press: New York, 1990. (g) Packer, L. Ed. *Methods in Enzymology* vol 90, Retinoids Part B; Academic Press: New York, 1991.

2. For nomenclature and numbering of retinoids, see: IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). *Eur. J. Biochem.* **1982**, *129*, 1.

3. Blomhoff, R.; Green, M. H.; Berg, T.; Norum, K. R. *Science* **1990**, *250*, 399.

4. (a) Rando, R. R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 461. (b) Nathans, J. *Biochemistry* **1992**, *31*, 4923. (c) Khorana, H. G. *J. Biol. Chem.* **1992**, *267*, 1. (d) Khorana, H. G. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1166. (e) Birge, R. R. *Annu. Rev. Biophys. Bioeng.* **1981**, *10*, 315. (f) Stoeckenius, W.; Bogomolni, R. A. *Annu. Rev. Biochem.* **1982**, *52*, 587. (g) Birge, R. R. *Biochim. Biophys. Acta* **1990**, *1016*, 293. (h) Rothschild, K. *J. Bioenerg. Biomembr.* **1992**, *24*, 147. (i) Oesterhelt, D.; Tittor, J.; Bamberg, E. *J. Bioenerg. Biomembr.* **1992**, *24*, 181. (j) Ebrey, T. Light Energy Transduction in Bacteriorhodopsin. In *Thermodynamics of Membranes, Receptors and Channels*; Jacobson, M. Ed.; CRC Press: Boca Raton, FL, 1993, pp. 353-387.

5. (a) Pfahl, M. The Steroid/Retinoid Receptor Superfamily and Retinoid Response Pathways. In *From Molecular Biology to Therapeutics*; Bernard, B. A.; Shroot, B. Eds.; Karger: Basel, 1993, pp. 83-93. (b) Pfahl, M. Retinoid Response Pathways In *Retinoids: From Basic Science to Clinical Applicatioins*; Livrea, M. A.; Vidali, G. Eds.; Birkhäuser: Basel, 1994, pp. 113-126.

6. (a) Buck, J.; Derguini, F.; Levi, E.; Nakanishi, K.; Hämmerling, U. *Science* **1991**, *254*, 1654. (b) Both enantiomers are equally active; see: Derguini, F.; Nakanishi, K.; Hämmerling, U.; Buck, J. *Biochemistry* **1994**, *33*, 623.

7. (a) Isler, O.; Huber, W.; Ronco, A.; Kofler, M. *Helv. Chim. Acta* **1947**, *30*, 1911. (b) Pommer, H. *Angew. Chem.* **1960**, *72*, 811. (c) Manchand, P. S.; Rosenberger, M.; Saucy, G.; Wehrli, P. A.; Wong, H.; Chambers, L.; Ferro, M. P.; Jackson, W. *Helv. Chim. Acta* **1976**, *59*, 387. (d) Chabardes, P.; Decor, J. P.; Varagnat, J. *Tetrahedron* **1977**, *33*, 2799.

8. (a) Solladié, G.; Girardin, A. *Tetrahedron Lett.* **1988**, *29*, 213. Solladié, G.; Girardin, A.; Métra. P. *Tetrahedron Lett.* **1988**, *29*, 209. Solladié, G.; Girardin, A.; Lang, G. *J. Org. Chem.* **1989**, *54*, 2620. Solladié, G.; Berl, V. *Bull. Soc. Chim. Fr.* **1993**, *130*, 568. (b) Otera, J.; Misawa, H.; Onishi, T.; Suzuki, S.; Fujita, Y. *J. Org. Chem.* **1986**, *51*, 3834. (c) Baraldi, P.

G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857. Baraldi, P. G.; Barco, A.; Benetti, S.; Guarneri, M.; Manfredini, S.; Pollini, G. P.; Simoni, D. *Tetrahedron Lett.* **1988**, *29*, 1307.

9. (a) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683. (b) de Lera, A. R.; Torrado, A.; Iglesias, B.; López, S. *Tetrahedron Lett.* **1992**, *33*, 6205. (c) Torrado, A.; Alvarez, R.; López, S.; de Lera, A. R. *Synthesis*, in press.

10. The use of demethylretinols in bioorganic stuides of the visual cycle has been described; see: (a) Law, W. C.; Kim, S.; Rando, R. R. *J. Am. Chem. Soc.* **1989**, *111*, 793. (b) Cañada, F. J.; Law, W. C.; Rando, R. R.; Yamamoto, T.; Derguini, F.; Nakanishi, K. *Biochemistry* **1990**, *29*, 9690.

11. For reviews on the synthetic chemistry of retinoids, see: (a) Liu, R. S. H.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931. (b) Dawson, M. I.; Hobbs, P. D. The Synthetic Chemistry of Retinoids. In *The Retinoids: Biology, Chemistry and Medicine*, 2nd ed.; Sporn, M. B.; Roberts, A. B.; Goodman, D. S. Eds.; Raven: New York, 1993, pp 5-178.

12. For reviews, see (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749. (c) Suzuki, A. *Pure Appl. Chem.* **1986**, *58*, 629. (d) Suzuki, A. *Top. Curr. Chem.* **1986**, *130*, 23. (e) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (f) Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221.

13. (a) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541. (b) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509. (c) Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2268.

14. (a) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456. (c) Brown, H. C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6075.

15. Uenishi, J.; Beau, J-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

16. (a) Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A. *J. Org. Chem.* **1980**, *45*, 2526. (b) Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1985**, *64*, 44. (c) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1.

17. Knochel, P. Carbometallation of Alkenes and Alkynes. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Semmelhack, M. F. Eds.; Pergamon Press: Oxford, 1991; Vol 4, chapter 4.4, pp 865-911.

18. Satoh, Y.; Serizawa, H.; Miyaura, N.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 1811.

19. (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.

20. Wipf, P.; Lim, S. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068.

21. (a) Uenishi, J.; Kawahama, R.; Tanio, A.; Wakabayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1438. (b) Hibino, J.; Matsubara, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 2151. (c) Matsubara, S.; Hibino, J.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Organomet. Chem.* **1985**, *285*, 163.

22. Gridnev, I. D.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 5351.

23. (a) Ganter, U. M.; Schmid, E. D.; Pérez-Sala, D.; Rando, R. R.; Siebert, F. *Biochemistry* **1989**, 28, 5954. (b) Cañada, F.

J.; Law, W. C.; Rando, R. R.; Yamamoto, T.; Derguini, F.; Nakanishi, K. *Biochemistry* **1990**, 29, 9690. (c) Weidlich, O.; Siebert, F. Sixth International Conference on Retinal Proteins; Leiden, The Netherlands, 19-24 June 1994, p. 171.

24. (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173. (b) For a closely-related procedure see: Bestmann, H. J.; Rippel, H. C.; Dostalek, R. *Tetrahedron Lett.* **1989**, *30*, 5261.

25. (a) van den Tempel, P. J.; Huisman, H. O. *Tetrahedron* **1966**, *22*, 293. (b) Blatz, P. E.; Lin, M.; Balasubramaniyan, P.; Balasubramaniyan, V.; Dewhurst, P. B. *J. Am. Chem. Soc.* **1969**, *91*, 5930. (c) Kropf, A.; Whittenberger, B. P.; Goff, S. P.; Waggoner, A. S. *Exp. Eye Res.* **1973**, *17*, 591. (d) Broek, A. D.; Muradin-Szweykowska, M.; Courtin, J. M. L.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 46. (e) van der Berg, E. M. M.; van der Bent, A.; Lugtenburg, *J. Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 160. (f) Duhamel, L.; Ple, G.; Ramondenc, Y. *Tetrahedron Lett.* **1989**, *30*, 7377.

26. Simmons, D. P.; Reichlin, D.; Skuy, D. *Helv. Chim. Acta* **1988**, *71*, 1000.

27. (a) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

28. (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370. (b) Suseela, Y.; Prasad, A. S. B.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1990**, 446. (c) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.

29. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

30. (a) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772. (b) Wulff, W. D.; Powers, T. S. *J. Org. Chem.* **1993**, *58*, 2381.

31. For preparation of (Z)-alkenylboronates see, Srebnik, M.; Bhat, N. G.; Brown, H. C. *Tetrahedron Lett.* **1988**, *29*, 2635, and references cited therein.

32. Coulson, D. R. *Inorg. Syn.* **1980**, *13*, 121.

33. Perrin, D. D.; Amarego, W. L. *Purification of Laboratory Chemicals*, 3rd. ed.; Pergamon: Oxford, 1988.

34. Broek, A. D.; Courtin, J. M. L.; Mellema, J. R.; Lugtenburg, J.; Nicolay, K.; Dijkstra, K.; Kaptein, R. *Org. Magn. Res.* **1982**, *19*, 105.

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