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Stereocontrolled synthesis of (*S*)-9-*cis*- and (*S*)-11-*cis*-13,14-dihydroretinoic acid

Belén Vaz, Rosana Alvarez *, Angel R. de Lera *

Departamento de Química Orgánica and CINBIO, Universidade de Vigo, Lagoas-Marcosende, 36310 Vigo, Spain

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ABSTRACT

The 9-*cis* and 11-*cis* stereoisomers of 13,14-dihydroretinoic acid with *S* configuration, (*S*)-**7** and (*S*)-**9**, respectively, have been synthesized stereoselectively. The former has been recently characterized as the first endogenous natural ligand of the retinoid X receptor (RXR). The Julia-Kocienski reaction of allyl sulfones and aldehydes was used as connective step and afforded the *Z* isomer of a trienyl ester accounting for the entire side chain of the targets. A highly selective and unidirectional iodine-induced isomerization of a *Z,Z,E* triene to the desired *E,Z,E* isomer was required prior to the synthesis of (*S*)-**7** via a Suzuki cross-coupling. The same approach to (*S*)-**9** led to substantial isomerization when the Suzuki cross-coupling was used as the last bond-forming reaction. As alternative, the two bond-forming steps were exchanged and the synthesis of (*S*)-**9** was completed using the *Z*-selective Julia-Kocienski reaction.

1. Introduction

Vitamin A (retinol, **1**) and its metabolites (native retinoids) are essential in many physiological processes, such as vision, immunity, the regulation of embryonic development, the control of cell differentiation, cell proliferation and apoptosis.[1] With the exception of vision, most of these cellular processes have been traditionally considered to be mediated by the binding (and activation) of vitamin A metabolites all-*trans*-retinoic acid **2** and its 9-*cis* isomer **3** to retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which are members of the nuclear receptor superfamily.[2–5]

In addition to *all-trans*-retinoic acid **2**, vitamin A is transformed into additional metabolites that collectively help establish a delicate control of the homeostasis of retinoid levels.[1,6] In this regard, a group of endogenous dihydroretinoids, including all-*trans*-13,14-dihydroretinoic acid **5**, have been recently added to the vitamin A metabolite pool.[7–9] It has been shown that the formation of **5** involves the formal hydrogenation of all-*trans*-retinol **1** mediated by the enzyme retinol saturase (RetSat)[10] and further two-stage oxidation of the polar group of **4** to metabolite **5** mediated by retinol dehydrogenases (ADH/SDR) and retinal dehydrogenases (RADH).[8,9] Naturally-occurring **5** was shown to be the *R* enantiomer, which is consistent with its higher binding affinity to RARs and trans-activation activity in comparison with its antipode.[8]

Some double bond stereoisomers of the parent polyene[6] also play fundamental roles in biological systems. The best known of those is 11-*cis*-retinal **6**, the chromophore of the visual pigments, which binds to the apoprotein opsin as a protonated Schiff base to trigger the visual cycle upon light absorption.[11] Fig 1.

More controversial is the endogenous presence of 9-*cis*-retinoic acid **3** in cells and tissues.[12] Although originally described in the liver and kidney,[13] and later in rat epididymal tissue and spermatozoa,[14] its detection in various organs has been questioned,[15–20] perhaps

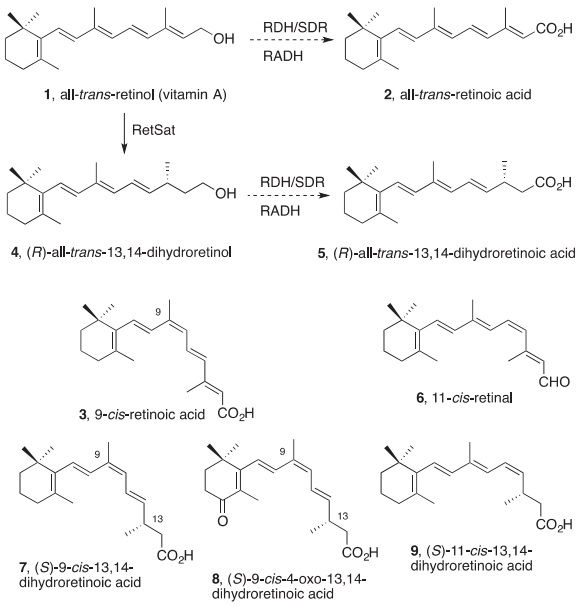

Fig. 1. Vitamin A**1** and selected metabolites of biological significance.

* Corresponding authors. Tel.: +34 986 812316; fax: +34 986 811940; e-mail addresses: rar@uvigo.es (R. Alvarez), qolera@uvigo.es (A.R. de Lera).

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with the exception of pancreas.[21,22] Pharmacological and genetic studies in mouse epidermis keratinocytes[23] and mouse embryos[24,25] added functional evidence to the analytical data and together concurred that 9-*cis*-retinoic acid **3** is unlikely a *bona fide* physiological ligand but rather a pharmacological ligand for both RARs and RXRs.[12]

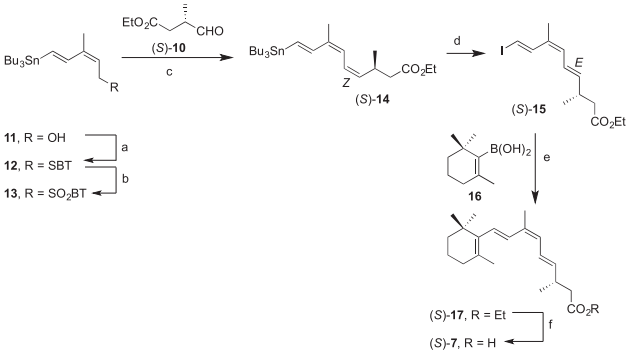
Studies of retinoid metabolism and gene expression are of major interest to aid in the identification of novel pathways regulated by yet uncharacterized endogenous ligands that can also alter gene expression.[6] Retinoid metabolites with 9-*cis* configuration, namely 9-*cis*-13,14-dihydroretinoic acid (*S*)-**7**[26] and its 4-oxo derivative (*S*)-**8**[27,28] have been recently isolated from several organs and characterized as retinoid receptor ligands. Although compounds with the structure of 9-*cis*-13,14-dihydroretinoic acid **7** (its absolute configuration was not determined) and its taurine conjugate were detected in rats, the animals had been fed with high doses of 9-*cis*-retinoic acid **3**, making interpretation of their putative role as an endogenous retinoid doubtful.[29] In contrast 9-*cis*-13,14-dihydroretinoic acid **7** was detected in normally fed animals, and found to bind and transactivate RXR (as well as RAR) in various assays and to display similar transcriptional activity as other RXR ligands in cultured human dendritic cells.[26] Intriguingly (*S*)-**8** was reported as an endogenous ligand for at least two RAR subtypes (α and β) but not for RXR. This compound induced in vivo morphological changes in chicken limb buds similarly to *all-trans*-retinoic acid **2** and regulated gene transcription in the same organ although with lower potency than **2**.[27,28] Thus far, the detailed metabolic pathway for formation of 9-*cis*-13,14-dihydroretinoids is unknown.

In order to aid in the characterization of endogenous retinoids, their metabolic formation and their function, we started a program aimed at the development of stereoselective approaches to dihydroretinoids of potential biological interest. We have reported the synthesis of all-*trans*-13,14-dihydroretinoic acid **5** in both enantiomeric forms and showed that the *R* enantiomer is the endogenous ligand.[8] The stereoselective synthesis of the *S* enantiomers (the configuration of the presumably oxidation metabolite **8**) of the 9-*cis* and 11-*cis* stereoisomers of this compound (**7** and **9**) is shown below.

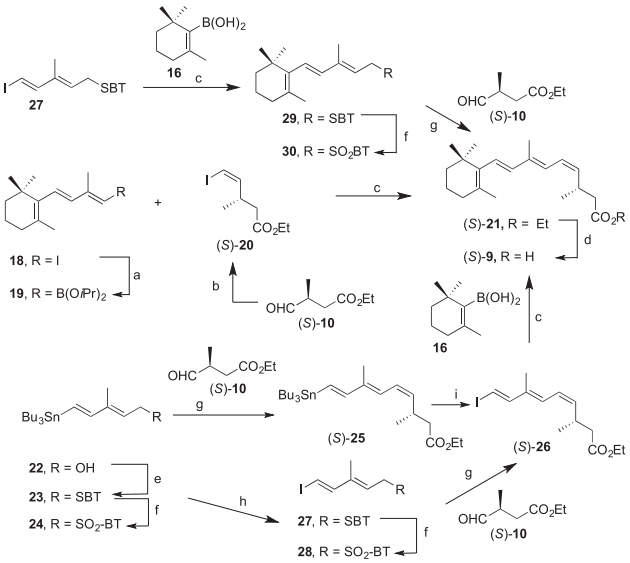
2. Results and discussion

Central to the construction of the polyene side chain of retinoids[1a] is the choice of the synthetic tactic. This may involve either the use of monofunctionalized components to perform Csp^2=Csp^2 bond construction by carbonyl condensation reactions (Wittig, HWE, Julia) or the use of mono and bis-functionalized alkenyl linchpins[30] to connect components of complementary reactivity by palladium-catalyzed Csp^2–Csp^2 cross-coupling reactions.[31] In practice, functionalized alkenyl reagents (as halogens or metal derivatives such as boron, tin, silicon, etc.) containing anion-stabilizing allyl groups (phosphonates, sulfones.) provide higher versatility to the synthetic scheme, as in general greater orthogonality is expected compared to the use of bis-functionalized alkenyl reagents.[32] Thus, the Suzuki cross-coupling reaction[33–35] was selected based on our previous comprehensive studies on the scope and limitations of this process for the synthesis of retinoids, and the findings that in general the reaction takes place with retention of configuration of the coupling partners,[36–40] whereas the Julia-Kocienski reaction[41,42] was considered for double bond formation starting from the corresponding functionalized components. For both targets, the disconnection of the C6–C7 bond by application of the Suzuki transform with cyclohexenyl boron derivative **16** and a trienyliodide was selected as key step. Prior to this step, the C11=C12 double bond was conceived to be formed by a Julia-Kocienski olefination[41–43] between a sulfone and the already described enantiopure aldehyde (*S*)-**10**,[8,44] which will be the source of the enantiopure compounds along the sequence.

For the preparation of (*S*)-9-*cis*-13,14-dihydroretinoic acid (*S*)-**7** the application of the Suzuki coupling reaction, as developed for the parent system,[39] requires the reaction of enantiopure trienyliodide (*S*)-**15** and boronic acid **16** (Scheme 1). The synthesis of (*S*)-**15** started with (*Z*)-stannyldienol **11**[39,45] which was transformed into the benzothiazolyl allyl sulfide **12** by Mitsunobu reaction with the corresponding thiol and subsequently oxidized to sulfone **13** with H_2O_2 and a peroxymolybdate reagent[46] at −10 °C (yields decreased at higher temperatures: 0 °C, 61%; 25 °C, 48%). The Julia-Kocienski olefination[41–43] was performed using a slight excess of base (NaHMDS, 1.15 equiv) and 1.7 equiv of enantiopure aldehyde (*S*)-**10**.[8,44] As anticipated from previous findings on the stereochemical outcome of the reactions between allyl sulfones and unsaturated aldehydes[47,48] the newly formed olefin of trienyl ester (*S*)-**14** is of *Z*-geometry, which was confirmed by NOE experiments. Treatment of the precursor stannane with a solution of iodine in CH_2Cl_2 produced the iodide (*S*)-**15** via Sn-I exchange and iodine-promoted isomerization of the *Z,Z,E* triene to the desired *E,Z,E* geometric isomer (as confirmed by NOE experiments). Immediate work-up and Suzuki reaction with the freshly prepared boronate **16**[39] afforded the expected ethyl (9*Z*)-13,14-dihydroretinoate (*S*)-**17** in good yield. Saponification of (*S*)-**17** led to the corresponding carboxylic acid (*S*)-**7** in good yield with preservation of the 9*Z* geometry of the tetraene.



Scheme 1. Reagents and conditions: (a) PPh_3, BTSH, DIAD, CH_2Cl_2, 25 °C, 2 h (95%). (b) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 30% H_2O_2, EtOH, −10 °C, 17 h (66%). (c) NaHMDS, THF, −78 °C, 30 min (93%). (d) I_2, CH_2Cl_2, 25 °C, 30 min (90%). (e) $Pd(PPh_3)_4$, 10% aq TlOH, THF, 25 °C, 3 h (78%). (f) 2M KOH, MeOH, 80 °C, 45 min; then H_3O^+ (84%).



Scheme 2. Reagents and conditions: (a) 1. *n*-BuLi, THF, −78 °C; 2. $B(O\text{-}i\text{-}Pr)_3$. (b) $IPPh_3CH_2I$, NaHMDS, THF, −78 °C; 2. (*S*)-**10**, THF, HMPA, −78 °C. (c) $Pd(PPh_3)_4$, 10% aq TlOH, THF, 25 °C, 3 h (15% for (*S*)-**21** from (*S*)-**20**; 71% for **29** from **27**; 33% for (*S*)-**21** from (*S*)-**26**). (d) 2M KOH, MeOH, 80 °C, 45 min; then H_3O^+ (91%). (e) PPh_3, BTSH, DIAD, CH_2Cl_2, 30 min (93% for **23**). (f) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 30% H_2O_2, EtOH, −10 °C, 17 h, 25 °C, 30 min (61% for **24**; 60% for **28**; 40% for **30**). (g) NaHMDS, THF, −78 °C, 30 min (89% for (*S*)-**25**; 89% for (*S*)-**21**; 34% for (*S*)-**26**). (h) NIS, CH_3CN, 0 °C, 1.5 h (84% for **27**). (i) I_2, CH_2Cl_2, 25 °C, 30 min (33% for (*S*)-**26**).

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As a first approach to the synthesis of the 11-*cis* isomer (*S*)-**9** we had considered a Suzuki coupling between the trienyl boronate **19** and the *Z*-vinyliodide (*S*)-**20**. However, the instability of both building blocks led us to complete the sequence without their isolation.[39] The *Z*-configured vinyliodide (*S*)-**20** was prepared successfully from the enantiopure aldehyde (*S*)-**10** through a Stork olefination. The crude reaction was immediately used in the next Suzuki coupling without further purification. Starting from the known trienyliodide precursor **18**,[38] the preparation of boronate **19** was carried out by treatment with *n*BuLi at −78 °C and subsequent reaction with B(O*i*Pr)$_3$. After 1 h, Pd(PPh$_3$)$_4$ was added followed by a solution of the *Z* iodide (*S*)-**20** obtained before in THF and, finally a 10% aqueous TlOH solution. This series of transformations provided the expected ethyl (11*Z*)-13,14-dihydroretinoate (*S*)-**21**, although in a disappointing 15% yield (Scheme 2).

An analogous synthetic route to the one developed for (9*Z*)-13,14-dihydroretinoic acid (*S*)-**7** was then explored. The *Z*-selective Julia-Kocienski olefination of allyl sulfones with aldehydes was selected,[47,48] and the Suzuki coupling was postponed to the last step to complete the assembly of the skeleton. Thus, the synthesis of the polyenic structure started from previously described *E*-stannyldienol **22** through its transformation into the benzothiazolyl sulfide **23** and subsequent oxidation to the desired sulfone **24**. The Julia-Kocienski olefination was performed as before with aldehyde (*S*)-**10**, giving rise exclusively to the trienyl ester (*S*)-**25** with *Z*-geometry of the newly formed double bond in 89% yield. During the subsequent Sn-I exchange, however, partial isomerization of the Z-olefin to the more stable all-*trans* triene was observed, as deduced from the analysis of the coupling constants in the ^{1}H NMR spectra. The ca. 1:1 mixture of isomeric trienyliodides (*S*)-**26** was subjected to the Suzuki coupling reaction conditions with **16**,[39] affording ethyl 13,14-dihydroretinoate (*S*)-**21** as a mixture of 11Z and all-*trans* isomers in the same ratio.

As the isomerization occurred during Sn-I exchange, we considered the possibility of running the one-pot Julia olefination with the iododienyl sulfone **28**, which was prepared from sulfide **27** (itself derived from the stannyldienol **22** in 93% yield using Mitsunobu conditions) in good yield following the same methodology described before, but adjusting the amount of oxidant to 10 equiv and using 0.2 mol equivalents of the peroxomolybdate reagent. Under the same conditions used before (100 mol equiv of 35% H_2O_2, 0.4 mol equiv $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$) the yield dropped to 23% and the dienyl sulfone was obtained as a mixture of isomers. Unfortunately, the trienyliodide (*S*)-**26** obtained by this route in 34% yield in the olefination reaction slowly isomerized to the all-*trans* isomer (1.7:1 *Z*/*E* ratio; significant changes were detected by ^{1}H NMR after 1 h, at which time a *Z*/*E* ratio of 1.4:1 was measured). Moreover, the Suzuki coupling of the mixture of iodides (*S*)-**26** with the corresponding cyclohexenylboronate **16** did not afford the expected ethyl retinoate (*S*)-**21**.

Finally, we decided to postpone the construction of the *Z*-olefin to the last step of the sequence. Therefore, the benzothiazolyl sulfide **23** was converted into the corresponding dienyliodide **27** by treatment with NIS in CH_3CN (99% yield) and subjected to the Suzuki coupling reaction with **16**, which produced the expected trienyl sulfide **29** in good yield (71%). Careful oxidation at 0 °C provided the all-*trans* trienyl sulfone **30**, although in moderate yield (40%). Finally, the *Z*-selective Julia-Kocienski reaction of **30** and (*S*)-**10** led to the expected tetraene (*S*)-**21** as a mixture of *Z*/*E* isomers in a 5:1 ratio, which were successfully separated by HPLC. Although saponification again required high temperatures (80 °C), the yield of (*S*)-**9** was satisfactory (91%) and the original 11*Z* geometry was preserved in the carboxylic acid (Scheme 2).

In summary we achieved the synthesis of (*S*)-9-*cis*-13,14-dihydroretinoic acid (*S*)-**7** and (*S*)-11-*cis*-13,14-dihydroretinoic acid (*S*)-**9** in a stereoselective manner, thus making these compounds available for further research. The synthetic routes are different to the approach to (*S*)-9-*cis*-4-oxo-13,14-dihydroretinoic acid (*S*)-**8** described previously.[49] Efforts are underway to uncover the occurrence and possible physiological functions of cis isomers other than the already validated retinoid receptor ligand (*S*)-**8**.

3. Experimental section

For general procedures, see Supplementary data.

3.1. (2*Z*,4*E*)-1-(Benzothiazol-2-yl)sulfanyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene 12

A solution of (2*Z*,4*E*)-3-methyl-5-(tri-*n*-butylstannyl)penta-2,4-dien-1-ol **11** (0.915 g, 2.36 mmol), 2-mercaptobenzothiazole (0.592 g, 3.54 mmol) and PPh_3 (1.10 g, 3.85 mmol) in THF (13 mL) was stirred for 5 min at 0 °C. A solution of DIAD (0.703 mL, 3.54 mmol) in THF (4.6 mL) was added dropwise and the mixture was stirred for 30 min at 25 °C. The solvent was removed and the residue was purified by column chromatography (silica gel, 97:3 hexane/Et_3N) to afford 1.20 g (95%) of a colorless oil identified as (2*Z*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene **12**. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.93 (d, *J*=8.2, 1H), 7.35 (d, *J*=19.1 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H), 7.10 (t, *J*=7.7 Hz, 1H), 6.90 (t, *J*=7.6 Hz, 1H), 6.55 (d, *J*=19.2 Hz, 1H), 5.54 (t, *J*=8.0 Hz, 1H), 4.26 (d, *J*=8.1 Hz, 2H), 1.75 (s, 3H), 1.67−1.52 (m, 6H), 1.44−1.30 (m, 6H), 1.04−0.89 (m, 15H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 166.6 (s), 154.1 (s), 142.8 (d), 138.8 (s), 135.9 (s), 132.3 (d), 126.2 (d), 124.3 (d), 122.3 (d), 121.9 (d), 121.2 (d), 30.8 (t), 29.6 (t, 3x), 27.8 (t, 3x), 20.0 (q), 14.0 (q, 3x), 9.9 (t, 3x) ppm. **IR** (NaCl): ν 2955 (s, C−H), 2923 (s, C−H), 2870 (m, C−H), 2850 (m, C−H), 1460 (s), 1427 (s) cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{25}H_{40}NS_2{}^{120}Sn$, 538.1620; found, 538.1621.

3.2. (2*Z*,4*E*)-1-(Benzothiazol-2-yl)sulfonyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene 13

To a solution of (2*Z*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene **12** (0.48 g, 0.89 mmol) in EtOH (9 mL), at −10 °C, was added a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, (0.44 g, 0.36 mmol) in aqueous hydrogen peroxide (35%, 7.7 mL, 89.1 mmol). After stirring for 17 h at −10 °C, the mixture was quenched with H_2O and extracted with Et_2O (3x). The combined organic layers were washed with brine (3x) and dried (Na_2SO_4), and the solvent was removed. The residue was purified by column chromatography (C18-silica gel, MeOH) to afford 0.33 g (66%) of a colorless oil identified as (2*Z*,4*E*)-1-(benzothiazol-2-yl)sulfonyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene **13**. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.99 (d, *J*=8.2 Hz, 1H), 7.07 (d, *J*=19.2 Hz, 1H), 7.05 (t, *J*=7.7 Hz, 1H), 7.01 (d, *J*=8.2 Hz, 1H), 6.87 (t, *J*=7.7 Hz, 1H), 6.48 (d, *J*=19.2 Hz, 1H), 5.32 (t, *J*=8.0 Hz, 1H), 4.21 (d, *J*=8.1 Hz, 2H), 1.63 (s, 3H), 1.62−1.54 (m, 6H), 1.45−1.33 (m, 6H), 1.02−0.93 (m, 15H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 166.5 (s), 152.3 (s), 142.6 (s), 141.2 (d), 136.42 (s), 133.9 (d), 126.8 (d), 126.6 (d), 124.5 (d), 121.7 (d), 111.6 (d), 53.1 (t), 29.2 (t, 3x), 27.4 (t, 3x), 19.9 (q), 13.7 (q, 3x), 9.6 (t, 3x) ppm. **IR** (NaCl): ν 2955 (s, C−H), 2923 (s, C−H), 2850 (m, C−H), 1467 (m), 1333 (s), 1151 (s) cm^{-1}. **HRMS** (ESI$^+$): *m*/*z* calcd for $C_{25}H_{39}NNaO_2S_2{}^{120}Sn$, 592.1338; found: 592.1334. **UV** (MeOH): λ_{max} 239 nm.

3.3. Ethyl (3*S*,4*Z*,6*Z*,8*E*)-3,7-dimethyl-9-(tri-*n*-butylstannyl) nona-4,6,8-trienoate (*S*)-14

A cooled (−78 °C) solution of (2*Z*,4*E*)-1-(benzothiazol-2-yl)sulfonyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene **13** (0.115 g, 0.20 mmol) in THF (9 mL) was treated with NaHMDS (0.23 mL, 1M

in THF, 0.23 mmol). After stirring for 30 min at this temperature, a solution of ethyl (*S*)-3-methyl-4-oxobutanoate (*S*)-**10** (0.044 g, 0.30 mmol) in THF (4.5 mL) was added and the resulting mixture was stirred for 1 h at −78 °C and then allowed to reach 25 °C for 3 h. Et_2O and water were added at low temperature and the mixture was warmed up to room temperature. It was then diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3x), the combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (C-18 silica gel, MeOH) to afford 0.94 g (93%) of a pale yellow oil identified as ethyl (3*S*,4*Z*,6*Z*,8*E*)-3,7-dimethyl-9-(tri-*n*-butylstannyl)nona-4,6,8-trienoate **14**. $[\alpha]_D^{28}$ +11.5 (*c* 1.22, MeOH). **^{1}H NMR** (400 MHz, C_6D_6): δ 7.50 (d, *J*=19.1 Hz, $^3J_{SnH}$=65.1 Hz, 1H), 6.74 (t, *J*=11.4 Hz, 1H), 6.54 (d, *J*=19.2 Hz, $^2J_{SnH}$=71.9 Hz,1H), 6.47 (d, *J*=11.9 Hz, 1H), 5.20 (t, *J*=10.4 Hz, 1H), 3.93 (q, *J*=7.1 Hz, 2H), 3.39−3.24 (m, 1H), 2.30−2.03 (m, 2H), 1.91 (s, 3H), 1.71−1.50 (m, 6H), 1.41−1.31 (m, 6H), 1.06−0.84 (m, 18H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 171.5 (s), 143.5 (d), 136.1 (d), 135.7 (s), 130.9 (d), 124.1 (d), 123.2 (d), 60.1 (t), 42.1 (t), 29.6 (t, 3x), 29.5 (d), 27.7 (t, 3x), 20.9 (q), 20.6 (q), 14.3 (q), 14.0 (q, 3x), 9.9 (t, 3x) ppm. **IR** (NaCl): ν 2957 (s, C−H), 2924 (s, C−H), 2871 (m, C−H), 2851 (m, C−H), 1737 (s, C=O), 1459 (m), 1160 (m) cm^{-1}. **HRMS** (ESI$^+$): *m/z* calcd for $C_{25}H_{46}NaO_2{}^{120}Sn$, 521.2416; found, 521.2408. **UV** (MeOH): λ_{max} 285 nm.

3.4. Ethyl (3*S*,4*E*,6*Z*,8*E*)-9-iodo-3,7-dimethylnona-4,6,8-trienoate (*S*)-15

To a solution of ethyl (3*S*,4*Z*,6*Z*,8*E*)-3,7-dimethyl-9-(tri-*n*-butylstannyl)nona-4,6,8-trienoate (*S*)-**14** (0.060 g, 0.120 mmol) in CH_2Cl_2 (5.3 mL) was added dropwise a solution of iodine (0.046 g, 0.180 mmol) in CH_2Cl_2 (2.8 mL) and the resulting mixture was stirred for 30 min at 25 °C. A saturated aqueous solution of $Na_2S_2O_3$ was added and the reaction mixture was extracted with Et_2O (3x), the combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 97:3 hexane/Et_3N) to afford 0.036 g (90%) of a pale yellow oil identified as ethyl (3*S*,4*E*,6*Z*,8*E*)-9-iodo-3,7-dimethylnona-4,6,8-trienoate (*S*)-**15**. $[\alpha]_D^{23}$ −16.7° (*c* 0.72, MeOH). **^{1}H NMR** (400 MHz, C_6D_6): δ 7.65 (d, *J*=14.5 Hz, 1H), 6.28 (dd, *J*=14.9, 11.3 Hz, 1H), 6.05 (d, *J*=14.5 Hz, 1H), 5.64 (d, *J*=11.1 Hz, 1H), 5.44 (dd, *J*=15.0, 7.8 Hz, 1H), 3.95 (q, *J*=7.1 Hz, 2H), 2.71−2.58 (m, 1H), 2.15 (dd, *J*=14.9, 7.1 Hz, 1H), 2.06 (dd, *J*=14.9, 7.3 Hz, 1H), 0.97 (t, *J*=7.2 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 171.9 (s), 142.7 (d), 140.4 (d), 132.7 (s), 130.9 (d), 124.6 (d), 78.5 (d), 60.5 (t), 41.8 (t), 34.5 (d), 20.4 (c), 19.9 (c), 14.7 (c) ppm. **IR** (NaCl): ν 2972 (m, C−H), 2932 (m, C−H), 1731 (s, C=O), 1666 (m), 1180 (m) cm^{-1}. **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{19}INaO_2$, 357.0322; found, 357.0316. **UV** (MeOH): λ_{max} 275 nm.

3.5. Ethyl (9*Z*,13*S*)-13,14-dihydroretinoate (*S*)-17

To a solution of ethyl (3*S*,4*E*,6*Z*,8*E*)-9-iodo-3,7-dimethylnona-4,6,8-trienoate (*S*)-**15** (0.036 g, 0.107 mmol) in THF (2.3 mL) was added $Pd(PPh_3)_4$ (0.013 g, 0.011 mmol). After 5 min at room temperature, 2,6,6-trimethylcyclohex-1-enylboronic acid **16** (0.027 g, 0.161 mmol) was added in one portion followed by TlOH (10% aqueous solution, 0.75 mL, 0.407 mmol). After stirring for 3 h at 25 °C, Et_2O was added and the reaction mixture was filtered through a short pad of Celite®. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ and the organic layer was dried (Na_2SO_4). The solvent was removed by evaporation and the residue was purified by column chromatography (silica gel, 97:3 hexane/Et_3N) to afford 0.028 g (78%) of a pale yellow oil identified as ethyl (9*Z*,13*S*)-13,14-dihydroretinoate (*S*)-**17**. $[\alpha]_D^{22}$ −15.5 (*c* 0.51, MeOH). **^{1}H NMR** (400 MHz, C_6D_6): δ 6.90 (d, *J*=16.0 Hz, 1H), 6.71 (dd, *J*=14.9, 11.2 Hz, 1H), 6.28 (d, *J*=16.0 Hz, 1H), 5.96 (d, *J*=11.1 Hz, 1H), 5.51 (dd, *J*=15.0, 7.8 Hz, 1H), 3.94 (q, *J*=7.2 Hz, 2H), 2.77 (dt, *J*=14.1, 7.1 Hz, 1H), 2.21 (dd, *J*=14.8, 7.3 Hz, 1H), 2.11 (dd, *J*=14.8, 7.2 Hz, 1H), 1.95 (t, *J*=6.1 Hz, 2H), 1.90 (s, 3H), 1.79 (s, 3H), 1.63−1.53 (m, 2H), 1.50−1.43 (m, 2H), 1.11 (s, 6H), 0.95 (t, *J*=7.1 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 171.6 (s), 138.5 (s), 137.9 (d), 133.0 (s), 130.9 (d), 129.3 (d), 129.2 (s), 128.2 (d), 127.9 (s), 125.1 (d), 60.0 (t), 41.8 (t), 39.8 (t), 34.5 (s), 34.4 (d), 33.2 (t), 29.2 (q, 2x), 22.0 (q), 20.7 (q), 20.3 (q), 19.7 (t), 14.4 (q) ppm. **IR** (NaCl): ν 2961 (s, C−H), 2929 (s, C−H), 2866 (m, C−H), 1737 (s, C=O), 1455 (m), 1372 (m), 1167 (m) cm^{-1}. **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{35}O_2$, 331.2632; found, 331.2625. **UV** (MeOH): λ_{max} 287 nm (ε=20,000 L mol^{-1} cm^{-1}).

3.6. (9*Z*,13*S*)-13,14-Dihydroretinoic acid (*S*)-7

To a solution of ethyl (9*Z*,13*S*)-13,14-dihydroretinoate (*S*)-**17** (0.023 g, 0.069 mmol) in MeOH (4.7 mL) was added KOH (2M aqueous solution, 1.1 mL, 2.27 mmol) and the reaction mixture was stirred for 45 min at 80 °C. After cooling down to 25 °C, CH_2Cl_2 and brine were added and the layers were separated. The aqueous layer was washed with H_2O (3x). The combined aqueous layers were acidified with 10% HCl and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, gradient from 95:5 to 90:10 CH_2Cl_2/MeOH) to afford 0.017 g (84%) of a pale yellow oil identified as (9*Z*,13*S*)-13,14-dihydroretinoic acid (*S*)-**7**. $[\alpha]_D^{24}$ −6.9 (*c* 0.26, MeOH). **^{1}H NMR** (400 MHz, $(CD_3)_2CO$): δ 6.66 (d, *J*=16.0 Hz, 1H), 6.60 (dd, *J*=15.0, 11.1 Hz, 1H), 6.18 (d, *J*=16.0 Hz, 1H), 5.93 (d, *J*=11.1 Hz, 1H), 5.65 (dd, *J*=15.0, 7.5 Hz, 1H), 2.73 (dt, *J*=13.2, 7.0 Hz, 1H), 2.40−2.24 (m, 2H), 2.05−1.99 (m, 2H), 1.91 (s, 3H), 1.72 (s, 3H), 1.66−1.57 (m, 2H), 1.53−1.43 (m, 2H), 1.08 (d, *J*=6.7 Hz, 3H), 1.03 (s, 6H) ppm. **^{13}C NMR** (100 MHz, $(CD_3)_2CO$): δ 173.5 (s), 138.9 (s), 138.8 (d), 133.4 (s), 131.1 (d), 129.8 (s), 129.7 (d), 128.5 (d), 125.4 (d), 41.8 (t), 40.3 (t), 34.9 (s), 34.6 (d), 33.6 (t), 29.4 (q), 22.1 (q), 20.7 (q), 20.6 (q), 20.0 (t) ppm. **IR** (NaCl): ν 2957 (s, C−H), 2923 (s, C−H), 2855 (m, C−H), 1709 (s, C=O), 1446 (m), 1290 (m) cm^{-1}. **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{31}O_2$, 303.2319; found, 303.2313. **UV** (MeOH): λ_{max} 289 nm (ε=17,600 L mol^{-1} cm^{-1}).

3.7. Ethyl (11*Z*,13*S*)-13,14-dihydroretinoate (*S*)-21

NaHMDS (0.43 mL, 1M in THF, 0.43 mmol) was added to a cooled (−78 °C) solution of (iodomethyl)triphenylphosphonium iodide (0.230 g, 0.43 mmol) in THF (8.0 mL). After stirring for 20 min at this temperature, HMPA (0.15 mL) was added followed by a solution of ethyl (*S*)-3-methyl-4-oxobutanoate (*S*)-**10** (0.050 g, 0.35 mmol) in THF (2.0 mL) and the resulting mixture was stirred for 1.5 h at −78 °C. Water was then added at low temperature and the mixture was warmed up to room temperature. It was then diluted with hexane and the layers were separated. The aqueous layer was extracted with hexane (4x), the combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue obtained was used without further purification in the following Suzuki reaction.

To a solution of (1′*E*,3′*E*)-2-(4-iodo-3-methylbuta-1′,3′-dienyl)-1,3,3-trimethylcyclohex-1-ene **18** (0.060 g, 0.190 mmol) at −78 °C was added *n*-BuLi (1.43 M in hexanes, 0.318 mL, 0.455 mmol) dropwise. After 20 min at this temperature, triisopropylborate (0.241 mL, 1.044 mmol) was added and the mixture was stirred for an additional 30 min at 25 °C. After this time, $Pd(PPh_3)_4$ (0.022 g, 0.019 mmol) was added and the reaction mixture was stirred for 5 min at 25 °C. Then, a solution of the iodide obtained above in THF (1.5 mL) was transferred via cannula to the reaction mixture followed by TlOH (10% aqueous solution, 1.2 mL, 0.722 mmol). The resulting mixture was stirred for 7 h before the reaction was diluted with Et_2O. The mixture was filtered through a short pad of Celite®

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and washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (silica gel, 97:3 hexane/Et_3N) to afford 0.009 g (15%) of a pale yellow oil identified as ethyl (11*Z*,13*S*)-13,14-dihydroretinoate (*S*)-**21**. $[\alpha]_D^{24}$ −52.5 (*c* 0.08, MeOH). **^{1}H NMR** (400 MHz, C_6D_6): δ 6.56 (d, *J*=11.9 Hz, 1H), 6.35 (t, *J*=11.4 Hz, 1H), 6.30 (d, *J*=16.1 Hz, 1H), 6.24 (d, *J*=16.1 Hz, 1H), 5.24 (t, *J*=10.4 Hz, 1H), 3.94 (q, *J*=7.1 Hz, 2H), 3.37–3.25 (m, 1H), 2.25–2.11 (m, 2H), 1.95 (t, *J*=6.3 Hz, 2H), 1.81 (s, 3H), 1.73 (s, 3H), 1.63–1.56 (m, 2H), 1.50–1.46 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 0.95 (t, *J*=7.2 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 171.5 (s), 138.9 (d), 138.3 (s), 136.2 (s), 136.2 (d), 129.0 (s), 127.0 (d), 125.6 (d), 124.7 (d), 60.1 (t), 42.2 (t), 39.9 (t), 34.5 (s), 33.2 (t), 29.8 (d), 29.2 (q), 21.9 (q), 20.9 (q), 19.8 (t), 14.3 (q), 12.4 (q) ppm. **IR** (NaCl): ν 2958 (s, C–H), 2925 (s, C–H), 2860 (m, C–H), 1737 (s, C=O), 1448 (m), 1170 (m) cm^{-1}. **HRMS** (ESI^+): *m/z* calcd for $C_{22}H_{35}O_2$, 331.2632; found, 331.2630. **UV** (MeOH): λ_{max} 290 nm (ε=23,600 L mol^{-1} cm^{-1}).

3.8. (11*Z*,13*S*)-13,14-Dihydroretinoic acid (*S*)-9

To a solution of ethyl (11*Z*,13*S*)-13,14-dihydroretinoate **21** (0.009 g, 0.028 mmol) in MeOH (2.0 mL) was added KOH (2M aqueous solution, 0.46 mL, 0.930 mmol) and the reaction mixture was stirred for 30 min at 80 °C. After cooling down to room temperature, CH_2Cl_2 and brine were added and the layers were separated. The aqueous layer was washed with H_2O (3x). The combined aqueous layers were acidified with 10% HCl and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, gradient from 95:5 to 90:10 CH_2Cl_2/MeOH) to afford 0.008 g (91%) of a pale yellow oil identified as (11*Z*,13*S*)-13,14-dihydroretinoic acid (*S*)-**9**. $[\alpha]_D^{26}$ −34.1 (*c* 0.1, MeOH). **^{1}H NMR** (400 MHz, $(CD_3)_2CO$): δ 6.42 (d, *J*=11.9 Hz, 1H), 6.33 (ddd, *J*=11.8, 10.5, 1.1 Hz, 1H), 6.21 (d, *J*=16.2 Hz, 1H), 6.17 (d, *J*=16.2 Hz, 1H), 5.35 (t, *J*=10.2 Hz, 1H), 3.29–3.11 (m, 1H), 2.29 (dd, *J*=7.1, 1.8 Hz, 3H), 2.03–1.98 (m, 2H), 1.91 (d, *J*=1.1 Hz, 3H), 1.70 (q, *J*=0.9 Hz, 3H), 1.66–1.59 (m, 2H), 1.50–1.45 (m, 2H), 1.06 (d, *J*=6.7 Hz, 3H), 1.03 (s, 3H), 1.02 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $(CD_3)_2CO$): δ 173.4 (s), 139.2 (d), 138.7 (s), 137.2 (d), 136.6 (s), 129.6 (s), 127.3 (d), 126.0, (d) 124.9 (d), 42.1 (t), 40.5 (t), 35.0 (s), 33.7 (t), 30.9 (d), 30.5 (q), 29.4 (q), 22.1 (q), 21.2 (q), 20.1 (t), 12.5 (q) ppm. **IR** (NaCl): ν 2957 (s, C–H), 2926 (s, C–H), 2860 (m, C–H), 1709 (s, C=O), 1449 (m), 1287 (m) cm^{-1}. **HRMS** (ESI^+): *m/z* calcd for $C_{20}H_{31}O_2$: 303.2319; found: 303.2313.

3.9. (2*E*,4*E*)-1-(Benzothiazol-2-yl)sulfanyl-5-iodo-3-methylpenta-2,4-diene 27

To a solution of (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene[50] **23** (0.231 g, 0.430 mmol) in CH_3CN (2.5 mL) at 0 °C, was added *N*-iodosuccinimide (0.126 g, 0.559 mmol) in one portion. After stirring for 1.5 h at 0 °C, the mixture was quenched with satd $Na_2S_2O_4$ and $NaHCO_3$(sat) and extracted with Et_2O (3x). The combined organic layers were washed with H_2O (1x) and dried (Na_2SO_4), and the solvent was removed. The residue was purified by chromatography (C18-silica, CH_3CN) to afford 0.158 g (99%) of a colorless oil identified as (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-5-iodo-3-methylpenta-2,4-diene **27**. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.89 (d, *J*=8.1 Hz, 1H), 7.24 (d, *J*=8.0 Hz, 1H), 7.10 (t, *J*=7.7 Hz, 1H), 6.91 (t, *J*=7.7 Hz, 1H), 6.76 (d, *J*=14.7 Hz, 1H), 5.90 (d, *J*=14.7 Hz, 1H), 5.33 (t, *J*=8.0 Hz, 1H), 3.78 (d, *J*=8.0 Hz, 2H), 1.31 (s, 3H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 166.1 (s), 153.9 (s), 148.7 (d), 138.4 (s), 135.9 (s), 127.0 (d), 126.3 (d), 124.5 (d), 121.9 (d), 121.3 (d), 76.8 (d), 31.0 (t), 11.6 (q) ppm. **IR** (NaCl): ν 3061 (w, C–H), 2954 (m, C–H), 2921 (m, C–H), 2854 (w, C–H), 1457 (s), 1424 (s), 994 (s) cm^{-1}. **HRMS** (ESI^+): *m/z* calcd for $C_{13}H_{13}INS_2$, 373.9529; found, 373.9528. **UV** (MeOH): λ_{max} 226, 257 nm.

3.10. (2*E*,4*E*)-1-(Benzothiazol-2-yl)sulfanyl-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-diene 29

To a solution of (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-5-iodo-3-methylpenta-2,4-diene **27** (0.042 g, 0.112 mmol) in THF (2.0 mL) was added $Pd(PPh_3)_4$ (0.013 g, 0.011 mmol). After 5 min at 25 °C, 2,6,6-trimethylcyclohex-1-enylboronic acid **16** (0.028 g, 0.168 mmol) was added in one portion followed by TlOH (10% aqueous solution, 0.8 mL, 0.427 mmol). After stirring for 15 h at 25 °C, Et_2O was added and the reaction mixture was filtered through a short pad of Celite®. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, the organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 97:3 hexane/Et_3N) to afford 0.028 g (71%) of a pale yellow oil identified as (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-diene **29**. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.92 (d, *J*=8.1 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H), 7.09 (t, *J*=7.7 Hz, 1H), 6.90 (t, *J*=7.6 Hz, 1H), 6.18 (d, *J*=16.2 Hz, 1H), 6.09 (d, *J*=16.2 Hz, 1H), 5.68 (t, *J*=8.1 Hz, 1H), 4.09 (d, *J*=8.1 Hz, 2H), 1.91 (t, *J*=6.1 Hz, 2H), 1.73 (s, 3H), 1.66 (s, 3H), 1.59–1.51 (m, 2H), 1.46–1.42 (m, 2H), 1.05 (s, 6H) ppm. **^{13}C NMR** (101 MHz, C_6D_6): δ 166.7 (s), 154.0 (s), 138.9 (s), 137.9 (s), 137.5 (d), 136.0 (s), 129.2 (s), 127.4 (d), 126.2 (d), 124.3 (d), 124.0 (d), 121.9 (d), 121.2 (d), 39.8 (t), 34.4 (s), 33.1 (t), 31.9 (t), 30.5 (q), 29.1 (q), 21.8 (q), 19.7 (t), 12.4 (q) ppm. **IR** (NaCl): ν 2958 (s, C–H), 2922 (s, C–H), 2852 (s, C–H), 1459 (m) cm^{-1}. **HRMS** (ESI^+): *m/z* calcd for $C_{22}H_{28}NS_2$, 370.1658; found, 370.1658. **UV** (MeOH): λ_{max} 225, 275 nm.

3.11. (2*E*,4*E*)-1-(Benzothiazol-2-yl)sulfonyl-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-diene 30

To a solution of (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-diene **29** (0.049 g, 0.137 mmol) in EtOH (1.4 mL) at 0 °C, was added a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, (0.033 g, 0.027 mmol) in aqueous hydrogen peroxide (35%, 0.2 mL, 2.5 mmol). After stirring for 2 h at 0 °C, the mixture was quenched with H_2O and extracted with Et_2O (3x). The combined organic layers were washed with brine (3x) and dried (Na_2SO_4), and the solvent was removed. The residue was purified by column chromatography (silica gel, 90:7:3 hexane/EtOAc/Et_3N) to afford 0.022 g (40%) of a pale yellow oil identified as (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfonyl-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-diene **30**. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.95 (d, *J*=8.2 Hz, 1H), 7.02 (t, *J*=8.1 Hz, 2H), 6.88 (t, *J*=7.8 Hz, 1H), 6.05 (d, *J*=16.2 Hz, 1H), 5.95 (d, *J*=16.2 Hz, 1H), 5.38 (t, *J*=8.1 Hz, 1H), 4.06 (d, *J*=8.1 Hz, 2H), 1.86 (t, *J*=6.2 Hz, 2H), 1.55 (s, 3H), 1.54–1.48 (m, 2H), 1.51 (s, 3H), 1.42–1.35 (m, 2H), 0.94 (s, 6H) ppm. **^{13}C NMR** (101 MHz, C_6D_6): δ 167.5 (s), 153.1 (s), 143.8 (s), 137.5 (s), 137.3 (s), 136.7 (d), 129.6 (s), 128.9 (d), 127.5 (d), 127.4 (d), 125.2 (d), 122.3 (d), 114.0 (d), 55.0 (t), 39.7 (t), 34.3 (s), 33.1 (t), 28.9 (q, 2x), 21.7 (q), 19.6 (t), 12.7 (q) ppm. **IR** (NaCl): ν 2956 (s, C–H), 2926 (s, C–H), 2864 (m, C–H), 1467 (m), 1330 (s), 1149.4 (s) cm^{-1}. **HRMS** (ESI^+): *m/z* calcd for $C_{22}H_{28}NO_2S_2$, 402.1556; found, 402.1555. **UV** (MeOH): λ_{max} 238, 275 nm.

3.12. Ethyl (11*Z*,13*S*)-13,14-dihydroretinoate (*S*)-21

A cooled (−78 °C) solution of (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfonyl-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-diene **30** (0.012 g, 0.030 mmol) in THF (1.5 mL) was treated with NaHMDS (0.034 mL, 1M in THF, 0.034 mmol). After stirring for 30 min at this temperature, a solution of ethyl (*S*)-3-methyl-4-

oxobutanoate (*S*)-**10** (0.007 g, 0.045 mmol) in THF (0.7 mL) was added and the resulting mixture was stirred for 1 h at −78 °C. Et_2O and water were added at low temperature and the mixture was warmed up to room temperature. It was then diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3x), the combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 97:3 hexane/Et_3N) to afford 0.009 g (89%) of a pale yellow oil identified as a 5:1 mixture of 11*Z*/11*E* isomers of ethyl (13*S*)-13,14-dihydroretinoate (*S*)-**21**. They were separated by HPLC (Prep Nova Pak Silica HR, 98:2 hexane/EtOAc, 3 mL/min; t_R (*Z*)=33 min; t_R (*E*)=35 min).

3.13. (2*E*,4*E*)-1-(Benzothiazol-2-yl)sulfonyl-5-iodo-3-methylpenta-2,4-diene 28

To a solution of (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfanyl-5-iodo-3-methylpenta-2,4-diene **27** (0.056 g, 0.152 mmol) in EtOH (1.6 mL) at 0 °C, was added a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, (0.037 g, 0.030 mmol) in aqueous hydrogen peroxide (35%, 0.24 mL, 2.742 mmol). After stirring for 13 h at 0 °C, the mixture was quenched with H_2O and extracted with Et_2O (3x). The combined organic layers were washed with brine (3x) and dried (Na_2SO_4), and the solvent was removed. The residue was purified by recrystallization from acetone/hexane affording 0.036 g (60%) of white crystals identified as (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfonyl-5-iodo-3-methylpenta-2,4-diene **28**. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.94 (d, *J*=8.1 Hz, 1H), 7.07 (d, *J*=7.5 Hz, 1H), 7.06 (t, *J*=7.5 Hz, 1H), 6.91 (t, *J*=7.7 Hz, 1H), 6.65 (d, *J*=14.7 Hz, 1H), 5.86 (d, *J*=14.7 Hz, 1H), 5.11 (t, *J*=8.1 Hz, 1H), 3.86 (d, *J*=8.1 Hz, 2H), 1.14 (s, 3H) ppm. **^{13}C NMR** (100 MHz, C_6D_6): δ 167.1 (s), 153.0 (s), 147.8 (d), 143.4 (s), 137.1 (s), 127.7 (d), 127.5 (d), 125.2 (d), 122.5 (d), 116.6 (d), 79.4 (d), 54.2 (t), 12.0 (q) ppm.

3.14. Ethyl (3*S*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(tri-*n*-butylstannyl) nona-4,6,8-trienoate (*S*)-25

A cooled (−78 °C) solution of (2*E*,4*E*)-1-(benzothiazol-2-yl)sulfonyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene[50] **24** (0.030 g, 0.053 mmol) in THF (2.4 mL) was treated with NaHMDS (0.061 mL, 1M in THF, 0.061 mmol). After stirring for 45 min at this temperature, a solution of ethyl (*S*)-3-methyl-4-oxobutanoate (*S*)-**10** (0.013 g, 0.090 mmol) in THF (1.2 mL) was added and the resulting mixture was stirred for 1 h at −78 °C. Et_2O and water were added at low temperature and the mixture was warmed up to room temperature. It was then diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3x), the combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (C18-silica, MeOH) to afford 0.024 g (89%) of a pale yellow oil identified as an ethyl (3*S*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(tri-*n*-butylstannyl)nona-4,6,8-trienoate (*S*)-**25.** **^{1}H NMR** (400 MHz, C_6D_6): δ 6.98 (d, *J*=19.2 Hz, 1H), 6.65 (d, *J*=11.7 Hz, 1H), 6.48 (d, *J*=19.2 Hz, 1H), 6.32 (t, *J*=11.7 Hz, 1H), 5.25 (t, *J*=10.4 Hz, 1H), 3.92 (q, *J*=7.1 Hz, 2H), 3.36–3.20 (m, 1H), 2.21–2.11 (m, 2H), 1.83 (s, 3H), 1.73–1.53 (m, 6H), 1.44–1.32 (m, 6H), 1.06–0.89 (m, 21H) ppm. **^{13}C NMR** (100 MHz, C_6D_6). δ 171.4 (s), 151.9 (d), 137.3 (s), 137.2 (d), 127.9 (d), 126.6 (d), 124.8 (d), 60.1 (t), 42.2 (t), 29.6 (t, 3x), 27.8 (t, 3x), 21.0 (q), 14.3 (q), 14.0 (q, 3x), 12.0 (q), 9.9 (t, 3x) ppm.

3.15. Ethyl (11*Z*,13*S*)-13,14-dihydroretinoate (*S*)-21

To a solution of ethyl (3*S*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(tri-*n*-butylstannyl)nona-4,6,8-trienoate (*S*)-**25** (0.019 g, 0.039 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C, was added dropwise a solution of iodine (0.012 g, 0.047 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 5 min at 25 °C, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_4$ solution and extracted with Et_2O (3x). The combined organic layers were dried (Na_2SO_4), and the solvent was removed. NMR analysis of the crude obtained showed a 1:1 ratio of *E*/Z isomers of the expected iodide. The mixture was used in the next Suzuki reaction without further purification.

To a solution of the mixture of iodides obtained above in THF (0.8 mL) was added $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol). After 5 min at 25 °C, 2,6,6-trimethylcyclohex-1-enylboronic acid **16** (0.010 g, 0.058 mmol) was added in one portion followed by TlOH (10% aqueous solution, 0.262 mL, 0.148 mmol). After stirring for 16 h at 25 °C, Et_2O was added and the reaction mixture was filtered through a short pad of Celite®. The filtrate was washed with satd $NaHCO_3$, the organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 97:3 hexane/Et_3N) to afford 0.004 g (33%) of a pale yellow oil identified as a 1:1 mixture of 11*Z*/11*E* isomers of ethyl (13*S*)-13,14-dihydroretinoate (*S*)-**21**.

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Supplementary data

Supplementary data (General procedures, HPLC separation, NOE experiments and copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds described in the text) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.05.006.

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