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Enantioselective synthesis of all of the stereoisomers of (*E*)-13,14-dihydroxyretinol (DHR)

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Abstract—The Stille cross-coupling of trienyliodide **4** and *E*-alkenylstannanes **5**, derived from enantioenriched diols obtained by a Sharpless asymmetric dihydroxylation (SAD), provides a convergent route to all stereoisomers of 13,14-dihydroxyretinol (DHR), an immunomodulator derived from vitamin A.

1. Introduction

Vitamin A (retinol **1**, Fig. 1)[1] serves as a prohormone in cells and organs, generating a diverse range of metabolites that regulate fundamental physiological processes including vision,[2] cell differentiation, cell proliferation and apoptosis,[3] development and immunity. These intracellular mediators arise through biosynthetic pathways that cause structural changes to retinol's functional group (oxidation level) or side-chain (double bond geometry, positional shifts involving allylic hydrogens and olefin oxidation). (14*R*)-14-Hydroxy-4,14-*retro*retinol **2** (14-HRR)[4] and dihydroxyretinol **3** (DHR),[5] the only vitamin A metabolites with additional hydroxyl groups on the side-chain, stimulate B-cell proliferation and T-cell activation. In vitro studies

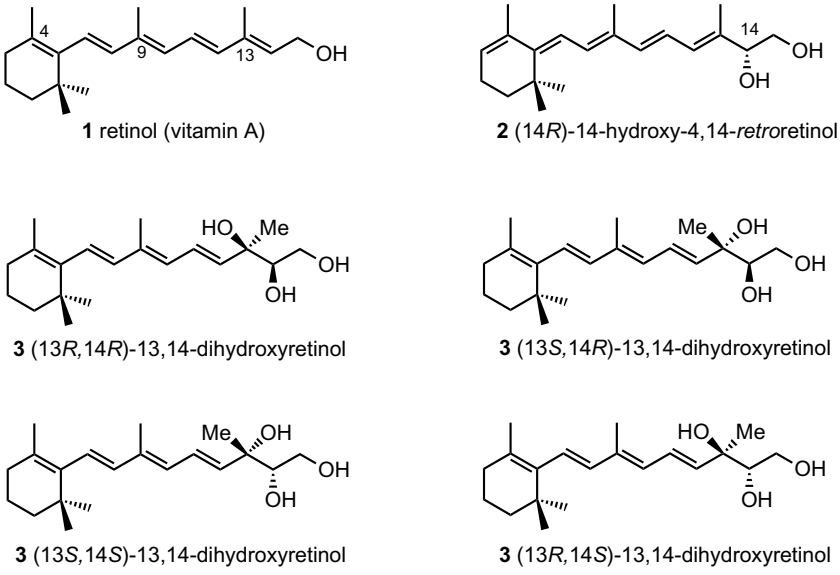

Figure 1. Retinol and its side-chain hydroxylated metabolites.

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using the 5/2 lymphoblastic cell line fed with ^{3}H-retinol proved the biogenetic relationship between vitamin A **1** and DHR **3**.[6] Interestingly, attempts to correlate biosynthetically DHR **3** and 14-HRR **2** in the same cell line proved unsuccessful, suggesting that both metabolites are independent end-points of retinol metabolism. An elusive 13,14-epoxyretinol might be the common precursor of both **2** and **3**.[6,7a]

Only one report on the non-stereoselective preparation of (13*R*,14*R*)-**3** and (13*S*,14*R*)-**3**, which uses D-glyceraldehyde acetonide as a chiral pool starting material, has so far been published.[5,7] On the other hand, Corey reported direct dihydroxylation of vitamin A acetate en route to metabolite **2**. This method afforded a 10:1 ratio of the primary to secondary acetate of (13*S*,14*S*)-**3**, due to scrambling by acetyl O,O-migration. The formation of the mixture was, however, inconsequential since the syntheses of **2** was completed by acetylation to give the 14,15-diacetate, dehydration, and saponification.[7c]

As part of our research concerned with the chemistry and biology of retinoids,[8] we required access to all DHR stereoisomers for immunomodulation studies. In our attempts to synthesize these target molecules, we set out to overcome some of the limitations of the existing route.[5] We envisioned that the preparation of **3** (Fig. 2) could be achieved through the combination of two powerful synthetic processes: (i) a metal-catalyzed cross-coupling[9] (a Stille reaction)[10] between stereodefined building-blocks **4** and **5** to control polyene geometry and (ii) the Sharpless enantioselective catalytic dihydroxylation (SAD)[11] of precursors **7** to enforce enantiofacial differentiation. The diversity-oriented combination of protected enynol isomers (*Z*)-**7** and (*E*)-**7** with pseudo-enantiomeric AD-mix α and AD-mix β reagents to obtain each of the four stereoisomers of target **3** is reported herein.

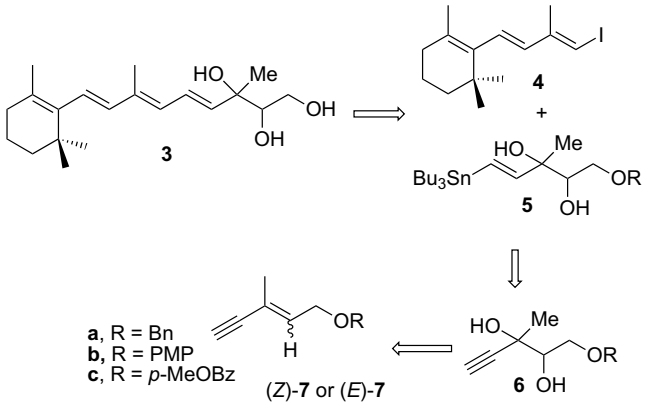


Figure 2.

2. Results and discussion

Benzyl ethers **7a** and *p*-methoxyphenyl ethers **7b** (derived from (*E*)- and (*Z*)-enynols by benzylation or Mitsunobu-type ether formation, respectively)[12] were reported by Tietze to afford the highest ee's in the dihydroxylation reaction using AD-mix α. Hence, these derivatives were selected to carry out our study. However, having obtained the desired skeleton, the protecting groups[13] proved to be quite robust and the more forcing conditions required, were incompatible with the stability of the final polyenic product. Among the base-labile protecting groups[13] the *p*-methoxybenzoates **7c** (prepared in high yields by stirring (*E*)- and (*Z*)-enynols with *p*-anisoyl chloride and Et_3N in CH_2Cl_2 at room temperature),[14] were selected because of their superior performance in SAD, relative to alcohols or ethers.[15]

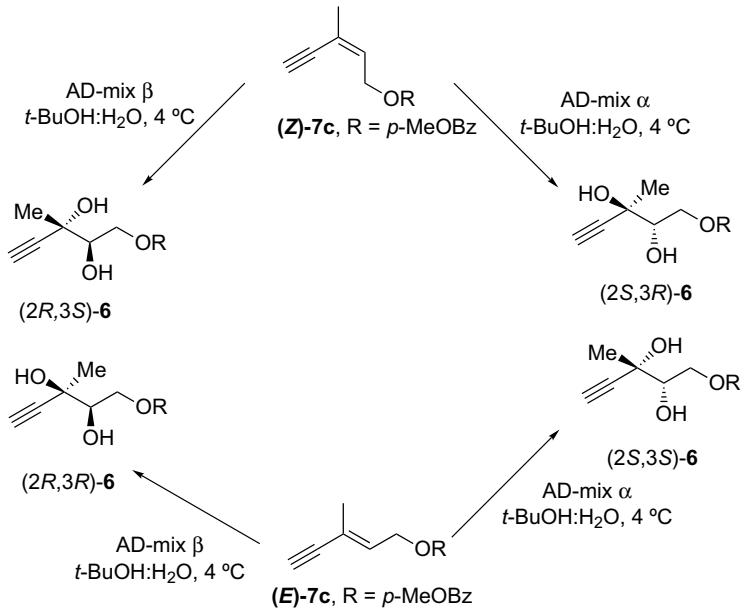
The yields and enantiomeric excesses for the dihydroxylation of enynols **7** are shown in Table 1. Analogues **7c** were first reacted with commercial AD-mix α and AD-mix β under standard reaction conditions (*t*-BuOH/H_2O, 4 °C), but significant amounts of starting material (up to 50%) were recovered after stirring for 48 h. We did however find that mixing the individual components of the SAD cocktail prior to running the reaction ensured completion of the dihydroxylation in the same period of time (Scheme 1).[16] According to the work of Sharpless[17] (*Z*)-trisubstituted enynes lead generally to lower ee's relative to the (*E*)-isomers. Strikingly, *p*-methoxybenzoate (*Z*-**7c** afforded the lowest ee (56%) when treated with the components of AD-mix α (entry 1).[18]

Two procedures for organostannane formation starting from alkynes, namely stannnylcupration/protonolysis[19] and palladium-catalyzed hydrostannation,[20] were then surveyed for the preparation of the alkenylstannanes (Scheme 2). The latter method [(*n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, 23 °C][19] afforded alkenylstannanes

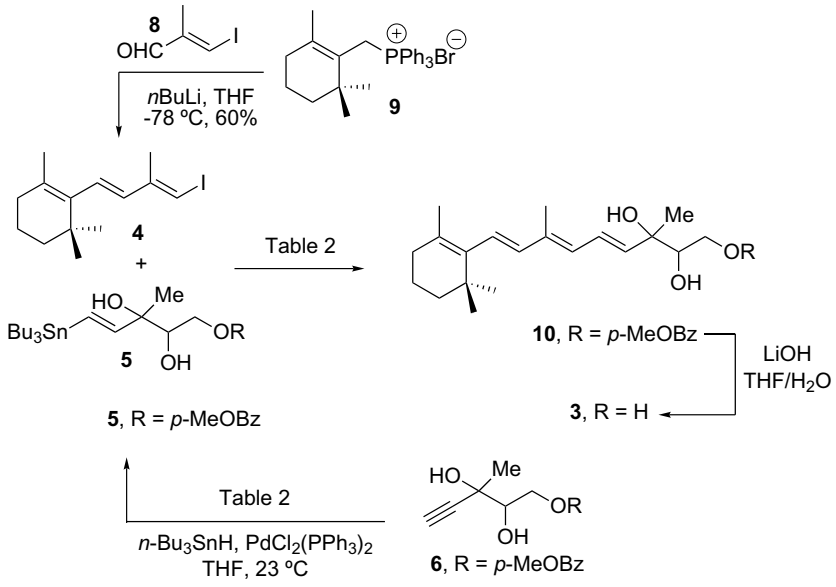
Table 1. SAD of protected enynols **7c** (Scheme 1)

Entry	Enyne	AD-mix[a]	Yield (%)[b]	Ee (%)[c]	Ee (%)[d]	Diol 6[e]
1	(*Z*)-**7c**	α	82	56	87	(2*S*,3*R*)-**6**
2	(*Z*)-**7c**	β	78	82	95	(2*R*,3*S*)-**6**
3	(*E*)-**7c**	α	74	86	96	(2*S*,3*S*)-**6**
4	(*E*)-**7c**	β	75	89	94	(2*R*,3*R*)-**6**

[a] Components of the AD-mix reagent in *t*-BuOH/H_2O, 4 °C, 48 h.
[b] Isolated product; average of three runs.
[c] The ee (%) was determined by chiral HPLC (Daicel Chiralcel OD-H, 15 cm × 0.46 cm) on the crude, unpurified reaction samples; average of three runs.
[d] The ee (%) was determined by chiral HPLC after purification by chromatography and crystallization (hexane/CH_2Cl_2).
[e] Absolute configuration of the major enantiomer assigned tentatively by application of the Sharpless mnemonic.



Scheme 1.



Scheme 2.

5 from the corresponding monoprotected triols in slightly higher yields (Table 2). A series of alkenylstannanes were subsequently coupled to trienyliodide **4**. Compound **4**, generally obtained by zirconium-assisted carboalumination–iodination starting from the dienyne derived from β-ionone, is a common building block in

Table 2. Yield (%) and enantiomeric excess (ee%) of the synthetic sequence starting from dihydroxylated enynols **6** (Scheme 2)

Configuration	**5** (%)[a]	**10** (%)[b]	Configuration	Ee **10** (%)[c]	**3** (%)[d]
(2*S*,3*R*)-**6**	60	73	(13*R*,14*S*)-**10**	88	85
(2*R*,3*R*)-**6**	50	75	(13*R*,14*R*)-**10**	94	95
(2*R*,3*S*)-**6**	80	77	(13*S*,14*R*)-**10**	96	99
(2*S*,3*S*)-**6**	61	75	(13*S*,14*S*)-**10**	94	95

[a] *n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, 25 °C.
[b] $(PhCN)_2PdCl_2$, *i*-Pr_2NEt, THF/DMF, 50 °C.
[c] Determined by chiral HPLC (Daicel Chiralcel OD-H, 15 cm × 0.46 cm).
[d] LiOH, THF/H_2O, 25 °C.

retinoid synthesis.[21] An alternative preparation that avoids the use of pyrophoric Me_3Al is the Wittig reaction between known aldehyde **8**[22] and the phosphonium salt **9**,[23] a process that furnishes **4** in comparable yield (Scheme 2).

The selection of Stille reaction conditions was guided by our previous experience in the synthesis of vitamin A and related polyenes.[8] The use of $(PhCN)_2PdCl_2$ in the presence of Hünig's base and a mixture of DMF/THF at 50 °C[24] offered slightly better yields than Farina's conditions (Pd_2dba_3, $AsPh_3$, NMP).[25] The yields for the purified polyenes are given in Table 2 along with the enantiomeric purity of **10**, as determined by chiral HPLC. Lastly, the stereoisomeric *p*-methoxybenzoates **10** were smoothly hydrolyzed by treatment with LiOH in THF/H_2O to provide triols **3** in high yields (Table 2). The enantiomeric excess of the final product **3** was inferred to be equal to that determined for the precursor *p*-methoxybenzoate **10**, since **3** suffered extensive decomposition on the chiral HPLC column.

3. Conclusion

In summary, SAD of protected enynols, palladium-catalyzed hydrostannation and Stille cross-coupling have been optimized in a synthetic sequence that afford every stereoisomer of DHR **3** with high enantiomeric purity after deprotection. Notably, the power of the Stille reaction for C–C bond formation in the presence of multiple free hydroxy groups should be highlighted.[26]

4. Experimental

4.1. General

All reactions were performed in an argon atmosphere. The solvents were dried and distilled under argon. HPLC grade solvents were used for the HPLC purification. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed using Merck silica gel 60 particle size (0.040–0.063 μm). Optical rotations were recorded on an Autopol IV polarimeter at the sodium D line. ^1H and ^{13}C magnetic resonance spectra (NMR) were recorded on Bruker AMX 400 [400 MHz (100 MHz for ^{13}C)]. Fourier transform spectrometers and chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) or chloroform ($CHCl_3$, 7.24 ppm for ^1H and 77.00 ppm for ^{13}C) as an internal reference. ^{13}C multiplicities (s, singlet; d, doublet; t, triplet; q, quartet) were assigned with the aid of the DEPT pulse sequence. Infrared spectra (IR) were obtained on a MIDAC Prospect Model FT-IR spectrophotometer. Absorptions are recorded in wavenumbers (cm^{-1}). UV spectra were recorded on a HP5989A spectrophotometer using MeOH as solvent. Absorption maxima are reported in nm. Low-resolution mass spectra were taken on a HP59970 instrument operating at 70 eV. High-resolution mass spectra were taken on a VG Autospec M instrument.

4.2. Preparation of *p*-methoxybenzoates

4.2.1. General procedure

4.2.1.1. (*E*)-3-Methylpent-2-en-4-in-1-yl *p*-methoxybenzoate (*E*)-7c. A solution of *p*-methoxybenzoyl chloride (10.64 g, 62.34 mmol) in CH_2Cl_2 (100 mL) was added to a solution of (*E*)-3-methylpent-2-en-4-in-1-ol (2.0 g, 20.82 mmol) and Et_3N (28.9 mL, 208.2 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred for 1 h at 25 °C and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 90:10 hexane/EtOAc) to afford 6.32 g (95%) of a white solid (mp 44–46 °C/hexane/EtOAc). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.98 (d, $J = 8.9$ Hz, 2H), 6.90 (d, $J = 8.9$ Hz, 2H), 6.12 (t, $J = 6.9$ Hz, 1H), 4.85 (d, $J = 6.9$ Hz, 2H), 3.85 (s, 3H), 2.87 (s, 1H), 1.92 (s, 3H) ppm. ^{13}C NMR (100.68 MHz, $CDCl_3$): δ 166.1 (s), 163.4 (s), 132.2 (d), 131.7 (d, 2×), 122.4 (s), 122.0 (s), 113.6 (d, 2×), 85.5 (s), 75.9 (d), 60.6 (t), 55.4 (q), 17.6 (q) ppm. FT-IR (NaCl): υ 3291 (m, C≡C), 2924 (m, C–H), 1711 (s, C=O), 1606 (s) cm^{-1}. MS (FAB^+): m/z (%) 232 (M^++2, 8), 231 (71), 230 (M^++1, 86), 164 (8), 154 (22), 153 (100). HRMS (FAB^+): calcd for $C_{14}H_{15}O_3$ (M^++1), 231.1021; found, 231.1023.

4.2.1.2. (*Z*)-3-Methylpent-2-en-4-in-1-yl *p*-methoxybenzoate (*Z*)-7c. Following the general procedure, the title compound was obtained from (*Z*)-3-methylpent-2-en-4-in-1-ol in 89% as a white solid (mp 40–42 °C/hexane/EtOAc) after purification by column chromatography (silica gel, 90:10 hexane/EtOAc). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.97 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.96 (t, $J = 6.7$ Hz, 1H), 4.96 (d, $J = 6.7$ Hz, 2H), 3.83 (s, 3H), 3.20 (s, 1H), 1.91 (s, 3H) ppm. ^{13}C NMR (100.68 MHz, $CDCl_3$): δ 166.1 (s), 163.3 (s), 132.5 (d), 131.6 (d, 2×), 122.5 (s), 122.0 (s), 113.6 (d, 2×), 82.9 (s), 81.4 (d), 63.04 (t), 55.4 (q), 21.9 (q) ppm. FT-IR (NaCl): υ 3291 (m, C≡C), 2927 (m, C–H), 2361 (m), 1711 (s, C=O) cm^{-1}. MS (FAB^+): m/z (%) 232 (M^++2, 6), 231 (M^++1, 48), 230 (M^+, 48), 155 (28), 1543 (100). HRMS (FAB^+): calcd for $C_{14}H_{15}O_3$ (M^++1), 231.1021; found, 231.1025.

4.3. Sharpless asymmetric dihydroxylation

4.3.1. General procedure

4.3.1.1. (2*S*,3*R*)-2,3-Dihydroxy-3-methylpent-4-yn-1-yl *p*-methoxybenzoate (2*S*,3*R*)-6. A solution of (*Z*)-3-methylpent-2-en-4-in-1-yl *p*-methoxybenzoate ***Z*-7c** (1.0 g, 4.35 mmol) in *t*-BuOH/H_2O (6 mL, 1:1, v/v) was added to an emulsion of $K_3Fe(CN)_6$ (4.29 g, 13.05 mmol), K_2CO_3 (1.80 g, 13.05 mmol), $(DHQ)_2PHAL$ (0.033 g, 0.044 mmol), $K_2OsO_4 \cdot 2H_2O$ (0.008 g, 0.022 mmol) and $MeSO_2NH_2$ (0.45 g,

4.78 mmol) in ^{t}BuOH/H_2O (6 mL, 1:1, v/v). The mixture was stirred at 5 °C, for 48 h, Na_2SO_3 (0.34 g) was added and the stirring maintained at 25 °C for 1 h. The mixture was extracted with CH_2Cl_2 (3×) and the organic layers washed with 1 M NaOH (3×), dried and concentrated. The residue was purified by column chromatography (silica gel, 65:35 hexane/EtOAc) and recrystallization to afford 0.945 g (82%) of a white solid (mp 80–82 °C/CH_2Cl_2/hexane) (56% ee on the crude; 87% ee after crystallization). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.99 (d, $J = 7.5$ Hz, 2H), 6.91 (d, $J = 7.5$ Hz, 2H), 4.59 (dd, $J = 12.1$, 3.1 Hz, 1H), 4.52 (dd, $J = 12.1$, 7.4 Hz, 1H), 3.86 (m, 4H), 3.01 (s, 1H), 2.95 (d, $J = 6.3$ Hz, 1H), 2.51 (s, 1H), 1.57 (s, 3H) ppm. ^{13}C NMR (100.13 MHz, $CDCl_3$): δ 167.1 (s), 163.9 (s), 132.0 (d, 2×), 122.2 (s), 113.9 (d, 2×), 84.4 (s), 76.4 (d), 74.0 (s), 69.4 (d), 66.3 (t), 55.7 (q), 26.2 (q) ppm. FT-IR (NaCl): υ 3418 (w, –OH), 2923 (m, CH═), 1708 (s, C═O), 1258 (s) cm^{-1}. MS (FAB$^+$): m/z (%) 266 (M$^+$+2, 14), 265 (M$^+$+1, 100), 247 (16), 195 (34), 154 (13). HRMS (FAB$^+$): calcd for $C_{14}H_{17}O_5$ (M$^+$+1), 265.1076; found, 265.1079. Anal. Calcd for $C_{14}H_{17}$: C, 63.61; H, 6.14. Found C, 63.64; H, 6.25. $[\alpha]_D^{25} = -25.6$ (c 0.42, MeOH).

4.3.1.2. (2*R*,3*S*)-2,3-Dihydroxy-3-methylpent-4-yn-1-yl *p*-methoxybenzoate (2*R*,3*S*)-6. Following the general procedure for the SAD (AD-mix β, method B), the title compound was obtained in 78% yield as a white solid after purification by column chromatography (silica gel, 65:35 hexane/EtOAc) and recrystallization (82% ee on the crude; 95% ee after purification). $[\alpha]_D^{25} = +32.9$ (c 0.37, MeOH).

4.3.1.3. (2*S*,3*S*)-2,3-Dihydroxy-3-methylpent-4-yn-1-yl *p*-methoxybenzoate (2*S*,3*S*)-6. Following the general procedure for the SAD (AD-mix α, method B), the title compound was obtained in 74% yield as a white solid after purification by column chromatography (silica gel, 65:35 hexane/EtOAc) and recrystallization (86% ee on the crude; 96% ee after purification) (mp 80–82 °C/CH_2Cl_2/hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.99 (d, $J = 6.7$ Hz, 2H), 6.90 (d, $J = 6.7$ Hz, 2H), 4.55 (dd, $J = 2.9$, 2.2 Hz, 1H), 4.50 (dd, $J = 6.9$, 2.5 Hz, 1H), 4.5–4.4 (m, 2H), 3.86 (s, 3H), 2.87 (s, 2H), 2.47 (s, 1H), 1.56 (d, $J = 2.2$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4 (s), 164.1 (s), 132.4 (d, 2×), 122.4 (s), 114.1 (d, 2×), 85.3 (s), 76.2 (d), 73.9 (s), 69.6 (d), 65.7 (t), 55.9 (q), 25.6 (q) ppm. FT-IR (NaCl): υ 3421 (w, OH), 2924 (m, C–H), 1696 (s), 1606 (f, C═O) cm^{-1}. MS (FAB$^+$): m/z (%) 265 (M$^+$+1, 6), 264 (M$^+$, 71), 164 (8), 154 (13), 153 (100). HRMS (FAB$^+$): calcd for $C_{14}H_{17}O_5$ (M$^+$+1), 265.1076; found, 265.1066. Anal. Calcd for $C_{14}H_{17}$: C, 63.61; H, 6.14. Found C, 63.71; H, 6.13. $[\alpha]_D^{25} = -28.7$ (c 0.74, MeOH).

4.3.1.4. (2*R*,3*R*)-2,3-Dihydroxy-3-methylpent-4-yn-1-yl *p*-methoxybenzoate (2*R*,3*R*)-6. Following the general procedure for the SAD (AD-mix β, method B) the title compound was obtained in 75% yield as a white solid after purification by column chromatography (silica gel, 65:35 hexane/EtOAc) and recrystallization (89% ee on the crude; 94% ee after purification) $[\alpha]_D^{25} = +29.9$ (c 1.27, MeOH).

4.4. Palladium-catalyzed hydrostannation

4.4.1. General procedure

4.4.1.1. (2*S*,3*R*,4*E*)-2,3-Dihydroxy-3-methyl-5-(tri-*n*-butylstannyl)-pent-4-yn-1-yl-*p*-methoxybenzoate (2*S*,3*R*)-5. Bu_3SnH (0.4 mL, 1.52 mmol) was added to a solution of (2*S*,3*R*)-2,3-dihydroxy-3-methylpent-4-yn-1-yl *p*-methoxybenzoate (2*S*, 3*R*)-**6** (0.2 g, 0.76 mmol) and $PdCl_2(PPh_3)_2$ (0.006 g, 0.015 mmol) in THF (20 mL). The reaction was stirred for 10 min and the solvent evaporated. The residue was purified by column chromatography (silica gel, 67:30:3 hexane/EtOAc/Et_3N) to afford 0.204 g (60%) of an oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.95 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.28 (d, $J = 19.5$ Hz, $^2J_{Sn-H} = 34.5$ Hz, 1H), 6.04 (d, $J = 19.5$ Hz, $^3J_{Sn-H} = 32.5$ Hz, 1H), 4.43 (dd, $J = 11.9$, 2.8 Hz, 1H), 4.27 (dd, $J = 11.9$, 7.6 Hz, 1H), 3.8–3.7 (m, 1H), 3.82 (s, 3H), 3.03 (s, 1H), 2.45 (s, 1H), 1.5–1.4 (m, 6H), 1.35 (s, 3H), 1.2–1.0 (m, 12H), 1.0–0.7 (m, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (s), 162.5 (s), 148.7 (d), 130.7 (d, 2×), 126.4 (d, $^1J_{Sn-C} = 174.2$ Hz), 121.2 (s), 112.6 (d, 2×), 74.8 (d, $^2J_{Sn-C} = 26.5$ Hz), 65.4 (t), 59.4 (s), 54.4 (q), 28.1 (t), 26.2 (t, $^2J_{Sn-C} = 27.3$ Hz), 23.9 (q), 12.7 (q), 8.4 (t, $^1J_{Sn-C} = 164.63$ Hz) ppm. MS (FAB$^+$): m/z (%) 555 (M$^+$+1, 9), 539 (24), 501 (21), 500 (25), 499 (100), 498 (42), 497 (76), 494 (41), 385 (32), 383 (24), 289 (20), 153 (33). HRMS (FAB$^+$): calcd for $C_{26}H_{45}O_5{}^{116}Sn$ (M+H$^+$), 555.2283; found, 555.2289. $[\alpha]_D^{25} = -14.8$ (c 0.027, MeOH).

4.4.1.2. (2*R*,3*S*,4*E*)-2,3-Dihydroxy-3-methyl-5-(tri-*n*-butylstannyl)-pent-4-yn-1-yl-*p*-methoxybenzoate (2*R*,3*S*)-5. Following the general procedure for hydrostannation with palladium, the title compound was obtained in 80% yield as a yellow oil after purification by column chromatography (silica gel, 67:30:3 hexane/EtOAc/Et_3N). $[\alpha]_D^{25} = +20.8$ (c 0.24, MeOH).

4.4.1.3. (2*S*,3*S*,4*E*)-2,3-Dihydroxy-3-methyl-5-(tri-*n*-butylstannyl)-pent-4-yn-1-yl-*p*-methoxybenzoate (2*S*,3*S*)-5. Following the general procedure for hydrostannation with palladium, the title compound was obtained in 61% yield as a yellow oil after purification by column chromatography (silica gel, 67:30:3 hexane/EtOAc/Et_3N). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.95 (d, $J = 9.1$ Hz, 2H), 6.87 (d, $J = 9.1$ Hz, 2H), 6.28 (d, $J = 19.5$ Hz, $^2J_{SnH} = 32.8$ Hz, 1H), 6.06 (d, $J = 19.5$ Hz, $^3J_{SnH} = 33.1$ Hz, 1H), 4.42 (dd, $J = 11.9$, 2.8 Hz, 1H), 4.27 (dd, $J = 11.9$, 7.6 Hz, 1H), 3.8–3.7 (m, 1H), 3.80 (s, 3H), 1.5–1.4 (m, 6H), 1.31 (s, 3H), 1.2–1.1 (m, 12H), 0.9-0.7 (m, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (s), 164.2 (s), 151.5 (d), 132.5 (d, 2×), 128.4 (d, $^1J_{Sn-C} = 174.3$ Hz), 122.9 (s), 114.4 (d, 2×), 76.2 (d, $^4J_{Sn-C} = 27.3$ Hz), 66.6 (t), 61.2 (s), 56.1 (q), 29.7 (t), 27.9 (t, $^2J_{Sn-C} = 27.3$ Hz), 23.7 (q), 14.9 (q), 10.2 (t, $^1J_{Sn-C} = 164.6$ Hz) ppm. MS (FAB$^+$): m/z (%) 555 (M$^+$+1, 13), 501 (30), 500 (2), 499 (100), 497 (60), 494 (40), 385 (20), 289 (50), 153 (33). HRMS (FAB$^+$): calcd

for $C_{26}H_{45}O_5{}^{116}Sn$ ($M+H^+$), 555.2266; found, 555.2260. $[\alpha]_D^{25} = -24.9$ (*c* 0.15, MeOH).

4.4.1.4. (2*R*,3*R*,4*E*)-2,3-Dihydroxy-3-methyl-5-(tri-*n*-butylstannyl)-pent-4-yn-1-yl-*p*-methoxybenzoate (2*R*,3*R*)-5. Following the general procedure for hydrostannation with palladium, the title compound was obtained in 50% yield as a yellow oil after purification by column chromatography (silica gel, 67:30:3 hexane/EtOAc/Et_3N). $[\alpha]_D^{25} = +12.5$ (*c* 0.008, MeOH).

4.4.2. 2-[(1*E*,3*E*)-4-Iodo-3-methylbuta-1,3-dien-1-yl]-1,3,3-trimethylcyclohex-1-ene 4. *n*-BuLi (4.6 mL, 1.5 M en hexane, 7.02 mmol) was added to a suspension of phosphonium salt **9** (3.0 g, 6.26 mmol) in THF (72 mL) at −30 °C, and the mixture stirred for 20 min at −30 °C, and for 40 min at −78 °C. A solution of iodide **8** (1.37 g, 7.02 mmol) in THF (24 mL) was then added. After 3 h stirring, H_2O (15 mL) was added and the mixture extracted with hexane (3×). The organic layers were dried and the solvent evaporated. The residue was purified by column chromatography (alumina, hexane) to afford 1.16 g (60%) of a yellow oil.[27]

4.5. Stille coupling

4.5.1. General procedure

4.5.1.1. (13*R*,14*S*)-13,14-Dihydroxyretinol *p*-methoxybenzoate (13*R*,14*S*)-10. To a solution of 2-[(1*E*, 3*E*)-4-iodo-3-methylbuta-1,3-dien-1-yl]-1,3,3-trimethylcyclohex-1-ene **4** (0.066 g, 0.208 mmol) in DMF (3.3 mL) was added a solution of (2*S*, 3*R*, 4*E*)-1-benzyloxy-5-(tri-*n*-butylstannyl)-3-methylpent-2-en-2,3-diol (2*S*, 3*R*)-**5** (0.050 g, 0.270 mmol) in THF (3.3 mL), $(PhCN)_2PdCl_2$ (0.024 g, 0.062 mmol) and *i*-Pr_2NEt (0.042 mL, 1.08 mmol). The mixture was stirred at 50 °C for 4 h. After addition of H_2O, the mixture was saturated with NaCl and extracted with CH_2Cl_2 (4×). The organic layers were dried and the solvent evaporated. The residue was purified by column chromatography (silica gel, 70:30 hexane/EtOAc) to afford 0.069 g (73%) of a solid (88% ee). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.96 (d, $J = 8.8$ Hz, 1H), 6.88 (d, $J = 8.8$ Hz, 1H), 6.72 (dd, $J = 15.2$, 11.3 Hz, 1H), 6.14 (d, $J = 15.7$ Hz, 1H), 6.02 (d, $J = 15.7$ Hz, 1H), 5.98 (d, $J = 11.3$ Hz, 1H), 5.74 (d, $J = 15.2$ Hz, 1H), 4.46 (dd, $J = 12.2$, 2.7 Hz, 1H), 4.3 (dd, $J = 12.7$, 7.7 Hz, 1H), 3.83 (s, 3H), 3.9–3.8 (m, 1H), 2.39 (s, 1H), 2.0–1.9 (m, 2H), 1.98 (s, 1H), 1.91 (s, 3H), 1.67 (s, 3H), 1.6–1.5 (m, 2H), 1.55 (s, 3H), 1.5–1.4 (m, 2H), 0.99 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (s), 163.6 (s), 137.8 (s), 137.4 (s), 136.5 (d), 134.6 (d), 131.8 (d, 2×), 129.2 (d), 128.7 (s), 127.2 (d), 126.2 (d), 122.1 (s), 113.7 (d, 2×), 76.1 (d), 74.4 (s), 66.3 (t), 55.4 (q), 39.5 (t), 34.2 (t), 31.6 (s), 29.1 (q), 28.9 (q), 22.6 (q), 21.7 (t), 14.1 (q) ppm. UV (MeOH): λ_{max} 290 (11,200) nm. MS (EI^+): *m*/*z* (%) 454 (M^+, 2), 259 (34), 152 (20), 147 (11), 135 (100), 92 (11), 91 (10), 76 (20) HRMS (EI^+): calcd for $C_{28}H_{38}O_5$, 454.2719; found, 454.2703. $[\alpha]_D^{25} = -22.7$ (*c* 0.022, MeOH).

4.5.1.2. (13*S*,14*R*)-13,14-Dihydroxyretinol *p*-methoxybenzoate (13*S*,14*R*)-10. Following the general procedure for Stille coupling, the title compound was obtained (75%) as a solid after purification by column chromatography (silica gel, 80:30 hexane/EtOAc) (96% ee). $[\alpha]_D^{25} = +27.7$ (*c* 0.018, MeOH).

4.5.1.3. (13*S*,14*S*)-13,14-Dihydroxyretinol *p*-methoxybenzoate (13*S*,14*S*)-10. Following the general procedure for Stille coupling, the title compound was obtained (75%) as a solid after purification by column chromatography (silica gel, 70:30 hexane/EtOAc) (94% ee). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.95 (d, $J = 8.9$ Hz, 2H), 6.87 (d, $J = 9.1$ Hz, 2H), 6.72 (dd, $J = 15.3$, 11.2 Hz, 1H), 6.13 (d, $J = 16.0$ Hz, 1H), 6.02 (d, $J = 15.8$ Hz, 1H), 5.99 (d, $J = 10.0$ Hz, 1H), 5.75 (d, $J = 15.3$ Hz, 1H), 4.46 (dd, $J = 11.9$, 3.1 Hz, 1H), 4.29 (dd, $J = 11.9$, 7.6 Hz, 1H), 3.82 (s, 3H), 3.9–3.8 (m, 1H), 2.74 (s, 2H), 2.0–1.9 (m, 2H), 1.91 (s, 3H), 1.67 (s, 3H), 1.6–1.5 (m, 2H), 1.54 (s, 3H), 1.5–1.3 (m, 2H), 0.98 (m, 6H) ppm. ^{13}C NMR (100.68 MHz, $CDCl_3$): δ 166.8 (s), 163.6 (s), 137.8 (s), 137.4 (d), 137.1 (s), 136.5 (d), 131.8 (d, 2×), 129.2 (s), 126.7 (d), 127.2 (d), 126.2 (d), 122.1 (s), 113.7 (d, 2×), 76.3 (s), 74.4 (d), 66.3 (t), 55.4 (q), 39.6 (t), 34.2 (s), 32.9 (t), 28.9 (q), 25.5 (q), 21.7 (q), 19.3 (t), 12.7 (q) ppm. UV (MeOH): λ_{max} 258 (11,000), 201 (11,500) nm. $[\alpha]_D^{25} = -16.6$ (*c* 0.036, MeOH). MS (EI^+): *m*/*z* (%) 454 (M^+, 10), 259 (30), 152 (30), 135 (100), 92 (11), 76 (30) HRMS (EI^+): calcd for $C_{28}H_{38}O_5$, 454.2710; found, 454.2708.

4.5.1.4. (13*R*,14*R*)-13,14-Dihydroxyretinol *p*-methoxybenzoate (13*R*,14*R*)-10. Following the general procedure for Stille coupling, the title compound was obtained (75%) as a solid after purification by column chromatography (silica gel, 80:30 hexane/EtOAc) (94% ee). $[\alpha]_D^{25} = +14.9$ (*c* 0.003, MeOH).

4.6. Hydrolysis

4.6.1. General procedure

4.6.1.1. (13*R*,14*S*)-13,14-Dihydroxyretinol (13*R*,14*S*)-3. $LiOH \cdot H_2O$ (0.01 g, 0.220 mmol) was added to solution of (13*R*,14*S*)-**10** (0.1 g, 0.220 mmol) in THF/H_2O (6 mL, 1:1, v/v). After stirring for 10 h, the mixture was neutralized with a solution of 10% citric acid and then extracted with EtOAc (3×). The organic layers were dried and the solvent evaporated. The residue was purified by column chromatography (silica gel, 60:40 hexane/EtOAc) to afford 0.059 g (85%) as a solid. ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.72 (dd, $J = 15.2$, 11.3 Hz, 1H), 6.16 (d, $J = 16.0$ Hz, 1H), 6.06 (d, $J = 11.9$ Hz, 1H), 6.05 (d, $J = 16.0$ Hz, 1H), 6.05 (d, $J = 15.2$ Hz, 1H), 3.8–3.6 (m, 2H), 3.6–3.5 (m, 1H), 2.5–2.4 (m, 2OH), 2.0–1.9 (m, 2H), 1.937 (s, 3H), 1.68 (s, 3H), 1.7–1.6 (m, 2H), 1.5–1.4 (m, 2H), 1.33 (s, 3H), 1.00 (s, 6H) ppm.[28] ^{13}C NMR (100.68 MHz, $(CD_3)_2CO$): δ 140.5 (d), 139.9 (d), 139.1 (s), 136.1 (s), 132.07 (d), 130.3 (s), 127.7 (d), 126.4 (d), 79.5 (d), 76.3 (s), 65.2 (t), 41.3 (t), 35.9 (s), 34.5 (t), 30.3 (q), 26.8 (q), 22.9 (q), 21.0 (t), 13.7 (q). UV (MeOH): λ_{max} 279 nm. MS (EI^+): *m*/*z* (%) 320 (M^+, 1), 306 (15), 278 (19), 277 (49), 259 (18), 234 (20),

233 (17), 226 (11), 152 (12), 137 (13), 123 (15), 121 (13), 109 (13), 97 (18), 95 (32), 83 (15), 81 (36), 71 (18), 69 (100), 67 (16). HRMS (EI^+): calcd for C_{20} H_{32} O_3, 320.2351; found, 320.2358. $[\alpha]_D^{25} = +9.9$ (*c* 0.04, MeOH).

4.6.1.2. (13*S*,14*R*)-13,14-Dihydroxyretinol (13*S*,14*R*)-3. Following the general procedure for hydrolysis, the title compound was obtained (99%) as a solid after purification by column chromatography (silica gel, 60:40 hexane/EtOAc) $[\alpha]_D^{25} = -13.3$ (*c* 0.03, MeOH).

4.6.1.3. (13*S*,14*S*)-13,14-Dihydroxyretinol (13*S*,14*S*)-3. Following the general procedure for hydrolysis, the title compound was obtained (95%) as a solid after purification by column chromatography (silica gel, 60:40 hexane/EtOAc). $[\alpha]_D^{25} = +14.3$ (*c* 0.06, MeOH).

4.6.1.4. (13*R*,14*R*)-13,14-Dihydroxyretinol (13*R*,14*R*)-3. Following the general procedure for hydrolysis the title compound was obtained (95%) as a solid after purification by column chromatography (silica gel, 60:40 hexane/EtOAc). ^{1}H NMR (400.13 MHz, $(CD_3)_2CO$): δ 6.73 (dd, $J = 15.2$, 11.3 Hz, 1H), 6.16 (d, $J = 16.1$ Hz, 1H), 6.12 (d, $J = 11.3$ Hz, 1H), 6.09 (d, $J = 16.2$ Hz, 1H), 5.92 (d, $J = 15.2$ Hz, 1H), 3.87 (s, 1H, OH), 3.8-3.6 (m, 3H), 2.1–2.0 (m, 2H),1.91 (s, 3H), 1.68 (s, 3H), 1.7–1.6 (m, 2H), 1.5–1.4 (m, 2H), 1.34 (s, 3H), 1.02 (s, 6H).[28] ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.74 (dd, $J = 15.2$, 11.3 Hz, 1H), 6.15 (d, $J = 16.1$ Hz, 1H), 6.07 (d, $J = 12.2$ Hz, 1H), 6.06 (d, $J = 16.1$ Hz, 1H), 5.75 (d, $J = 15.1$ Hz, 1H), 3.78 (m, 2H), 3.6–3.5 (m, 1H), 2.6–2.4 (m, OH), 2.04 (s, 3H), 2.0–1.9 (m, 2H), 1.69 (s, 3H), 1.7–1.6 (m, 2H), 1.5–1.4 (m, 2H), 1.01 (s, 6H) ppm.[28] ^{13}C NMR (100.68 MHz, $CDCl_3$): δ 137.8 (s), 137.4 (d), 136.6 (s), 136.4 (d), 129.5 (s), 128.5 (d), 127.3 (d), 126.2 (d), 76.4 (d), 74.9 (s), 63.0 (t), 39.6 (t), 34.2 (s), 33.0 (t), 29.0 (q, 2×), 24.0 (q), 21.7 (q), 19.3 (t), 12.7 (q). UV (MeOH): λ_{max} 289 nm. MS (EI^+): *m*/*z* (%) 259 (13), 256 (19), 137 (14), 129 (13), 97 (161), 95 (19), 93 (10), 85 (12), 83 (24), 82 (13), 72 (31), 71 (20), 70 (15), 69 (100). HRMS (EI^+): calcd for $C_{20}H_{32}O_3$, 320.2351; found, 320.2337. $[\alpha]_D^{25} = -11.5$ (*c* 0.026, MeOH).

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