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Synthesis of C11-to-C14 methyl-shifted all-*trans*-retinal analogues and their activities on human aldo-keto reductases†

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Human aldo-keto reductases (AKRs) are enzymes involved in the reduction, among other substrates, of all-*trans*-retinal to all-*trans*-retinol (vitamin A), thus contributing to the control of the levels of retinoids in organisms. Structure–activity relationship studies of a series of C11-to-C14 methyl-shifted (relative to natural C13-methyl) all-*trans*-retinal analogues as putative substrates of AKRs have been reported. The synthesis of these retinoids was based on the formation of a C10–C11 single bond of the pentaene skeleton starting from a trienyl iodide and the corresponding dienylstannanes and dienylsilanes, using the Stille–Kosugi–Migita and Hiyama–Denmark cross-coupling reactions, respectively. Since these reagents differ by the location and presence of methyl groups at the dienylorganometallic fragment, the study also provided insights into the ability of the different positional isomers to undergo cross-coupling and the sensitivity of these processes to steric hindrance. The resulting C11-to-C14 methyl-shifted all-*trans*-retinal analogues were found to be active substrates when tested with AKR1B1 and AKR1B10 enzymes, although relevant differences in substrate specificities were noted. For AKR1B1, all analogues exhibited higher catalytic efficiency (k_{cat}/K_m) than parent all-*trans*-retinal. In addition, only all-*trans*-11-methyl-retinal, the most hydrophobic derivative, showed a higher value of k_{cat}/K_m = 106 000 ± 23 200 mM^{-1} min^{-1} for AKR1B10, which is in fact the highest value from all known retinoid substrates of this enzyme. The novel structures, identified as efficient AKR substrates, may serve in the design of selective inhibitors with potential pharmacological interest.

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Introduction

Vitamin A **1a** (retinol) and its analogues with variation in the functional group and double bond geometries, collectively termed retinoids, play essential roles in many physiological processes, such as vision, cell differentiation, proliferation and apoptosis, immunity and the regulation of embryonic development.[1–3] In vision, 11-*cis*-retinal is the photochemically active retinoid which functions as an inverse agonist binding to a lysine residue of the apoprotein opsin, a G protein-coupled receptor, *via* a protonated Schiff base, and undergoes photochemical isomerization to the all-*trans* isomer.[4] In a similar structural arrangement, the light-driven proton-pump of microorganisms, termed bacteriorhodopsin, gets activated when all-*trans*-retinal as a photoactive chromophore bound to a lysine residue undergoes isomerization to the 13-*cis* isomer and promotes proton-pumping and related activities.[5] However, most of the above-mentioned processes taking place in cells and organisms are mediated by the binding (and consequent gene regulation) of vitamin A metabolites all-*trans*-retinoic acid (and also 9-*cis*-13,14-dihydroretinoic acid)[6] and 13-*cis*-retinoic acid to retinoic acid receptors (RARs) and retinoid X receptors (RXRs).[7] The activities of a series of retinoid-metabolizing enzymes[2] generate additional metabolites and jointly establish a delicate control of the homeostasis of retinoids in cells and organisms.[3]

In order to examine from the structural and functional perspectives the activities associated with biological systems containing retinoids as ligands, access to these unstable polyenes,

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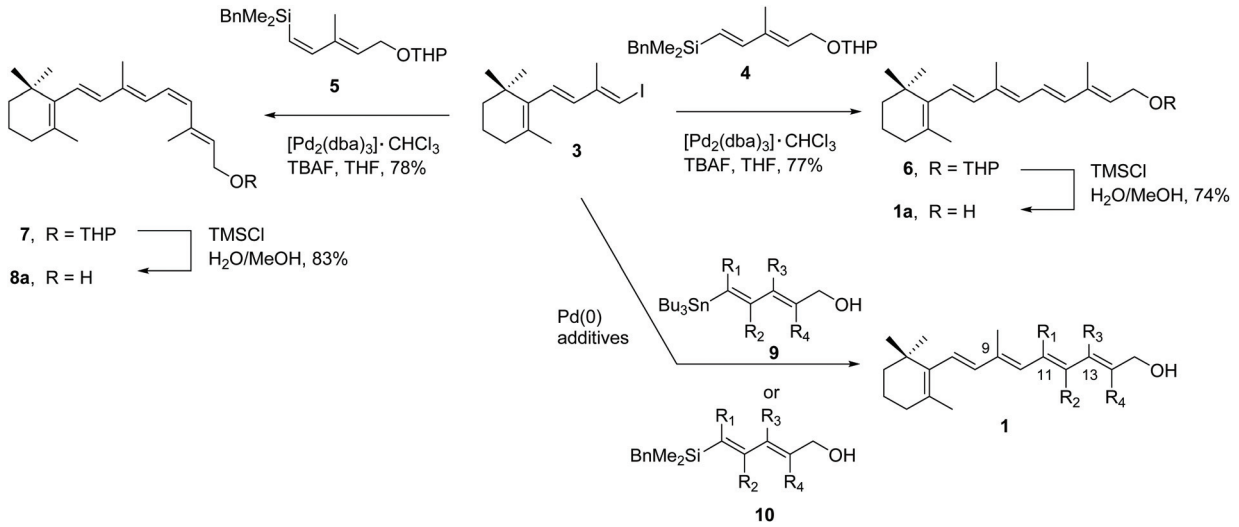
† Electronic supplementary information (ESI) available: General procedures, synthesis of intermediates, spectral characterization data for the products described in the text, including copies of the NMR spectra, expression and purification of AKR1B1 and HPLC enzymatic activity assay. See DOI: 10.1039/d0ob01084g



Scheme 1 The stereoselective synthesis of *all-trans*- and 11-*cis*-retinol (**1a** and **8a**, respectively) by the C_{14} + C_6 Hiyama–Denmark cross-coupling reaction of trienyliodide **3** and dienylsilanes **4** and **5**, respectively, followed by deprotection,[17] and an approach to the C11-to-C13 (de)methylated vitamin A analogues using dienylstannane **9** and dienylsilane **10**.

both natural and synthetically modified analogues, is required. A drawback in this field is the instability of these polyenes to light and oxygen, in addition to acidic and basic media, which becomes challenging when control of the double-bond geometries (namely, all-*trans*-, 9-*cis*-, 11-*cis*-, or 13-*cis*-isomers of selected retinoids) is required in order to undertake specific biological studies.

Synthetic approaches to the construction of the polyunsaturated skeleton of retinoids, as prototypes of highly conjugated polyenes, is currently based on the use of palladium-catalyzed Csp^2–Csp^2 cross-coupling reactions,[8] which in general take place with retention of the configuration of the coupling partners, thus surpassing the main limitations associated with alternative methods that rely on Csp^2=Csp^2 condensation reaction (Wittig, Horner–Wadsworth–Emmons, and Julia–Kocienski).[3,9] The Stille–Kosugi–Migita cross-coupling reaction[10] has been comprehensively used for the synthesis of retinoids (and carotenoids), and these synthetic challenges have illustrated the scope and limitations of this process for the preparation of highly unstable polyenes.[3]

On the other hand, the Hiyama–Denmark cross-coupling reaction[11–13] involves the use of organosilicon reagents,[14] which are in general easier to prepare and handle, and more stable and less toxic than organometallic compounds. Thus, they are already finding useful applications in the synthesis of polyenes,[13] including symmetrical and non-symmetrical undecaenes in carotenoids as recently shown by the bidirectional cross-coupling of central 1,3,5,7,9-pentaenylbissilanes with terminal trienyliodides.[15]

The Hiyama–Denmark cross-coupling reaction has been reported to be an alternative useful protocol for the efficient preparation of the common natural skeletons of retinoids, including the 11-*cis*- and all-*trans*-isomers.[16,17] Among a wide variety of heteroatom-functionalised silicon moieties, oxysilanes, cyclic silyl ethers, silanols and "safety-catch" derivatives were found to couple with almost the same efficiency under mild reaction conditions and provided 11-*cis*- and all-*trans*-retinol isomers (**8a** and **1a**, Scheme 1) as exemplified for benzyldimethylsilanes **5** and **4**, respectively (Scheme 1) in high yields.[16,17]

We are interested in understanding the structural dependence of the biological activities of retinoids[18,19] as substrates of retinoid-metabolizing enzymes.[2] The aldo-keto reductase (AKR) enzyme superfamily is considered to play a relevant role in retinoid metabolism, specifically the human enzymes aldose reductase AKR1B1 and aldose reductase-like AKR1B10. These two enzymes share a 71% amino acid sequence identity but their substrate specificity is quite different.[20] Upregulation of these AKRs has been observed in several pathologies such as cancer, inflammatory processes and diabetes. Thus, the development of potent and selective inhibitors has been extensively pursued.[21] Here we report the synthesis and use of substrate analogues of these enzymes, which may help exploring their active site architecture in order to design novel inhibitors with potential use as therapeutic agents. We have already reported the enzymatic activities of AKRs with retinal derivatives modified at the trimethylcyclohexenyl ring.[22] As a follow-up of these studies, we required access to a series of analogues of all-*trans*-retinal that differ in the presence/absence and positional relocation of the methyl substituent at C13 (Scheme 1) in order to test them as substrates for AKRs.

Given the recently reported study on the scope of the Hiyama–Denmark cross-coupling reaction for the synthesis of the natural all-*trans*- and 11-*cis*-retinoids and analogues using the highly convergent C_{14} + C_6 strategy (Scheme 1),[16,17] we decided to examine this cross-coupling variant in parallel to the Stille–Kosugi–Migita reaction for the construction of the

central C11–C12 single bond as synthetic approaches to these C13-methyl-shifted pentaenes.[16,17]

Results and discussion

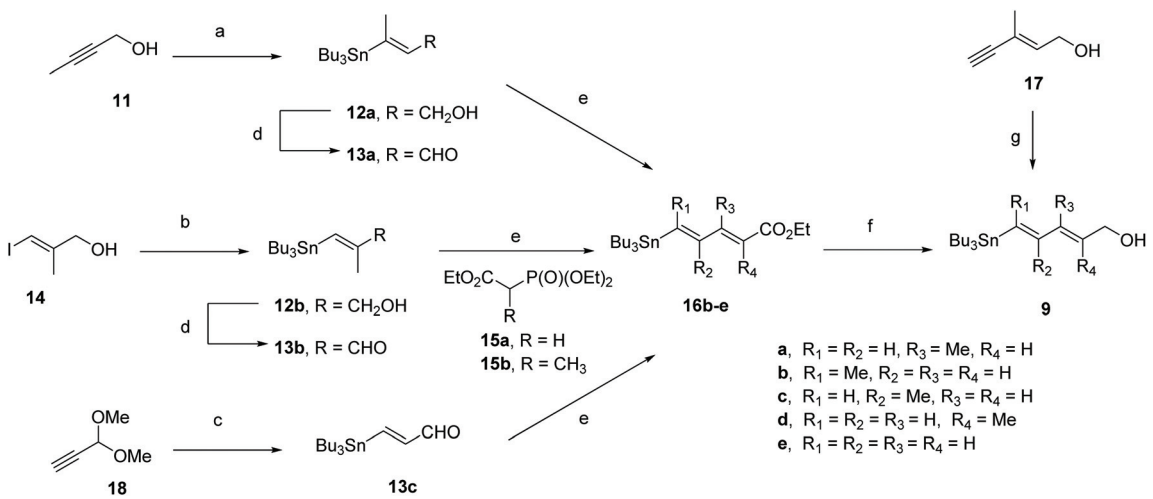
Alkenylorganometallic reagents are routinely prepared from alkynes by regio- and stereoselective hydrometallation, carbometallation, halometallation, and metallometallation reactions.[23] With all these transformations, as well as the ensuing metal–halogen exchange processes, which are highly stereoselective, a wide collection of alkenyl organometallic reagents and alkenyl halides with different substitution patterns can be explored in Pd-catalyzed cross-coupling reactions.

Regarding the Stille–Kosugi–Migita cross-coupling, dienylstannanes **16** have been previously reported with the exception of **16c**. For the sake of completeness, their preparation is detailed in Scheme 2, which collects the entire series of functionalized stannylpentadienols **9** and stannylpentadienyl esters **16** following the precedent work.

Aldehyde **13a** was prepared by regio- and stereoselective stannylcupration/protonolysis (99% yield) of but-2-yn-1-ol **11**,[24] followed by allylic oxidation of **12a** with MnO_2 and Na_2CO_3 (92%). Positional isomer **13b**[25] was obtained from the precursor iodide **14**[26] by alcohol protection (TBSCl, Et_3N, 97%), followed by iodine–tin exchange (*t*-BuLi, Bu_3SnCl, 77%), deprotection (TBAF, 92%) and allylic oxidation (MnO_2, Na_2CO_3, 92%). β-Tributylstannylacrolein **13c** was synthesized in good overall yield (82% combined) by stereoselective stannylcupration of 3,3-dimethoxyprop-1-yne **18** (Bu_3SnH, *n*-BuLi, CuCN, and MeOH) and deprotection of the dimethyl acetal (*p*-TsOH and acetone-H_2O, 80 °C).[27,28] Tributylstannylpenta-2,4-dienoates **16b–e** were prepared in good yields (73–92%) by the stereoselective Horner–Wadsworth–Emmons reaction of aldehydes **13a–c** and the phosphonate anions (*n*-BuLi, DMPU, and THF) derived from either triethyl phosphonoacetate **15a**[27] or ethyl 2-(diethoxyphosphoryl)-propanoate **15b**. The dienoates **16b–e** were reduced with Dibal-H to afford stannyldienols **9b–e** in good overall yields (68–99%), in accordance with previous reports (**9e**,[29] **9c**,[30] and **9d**[28]). Lastly, the synthesis of 3-methyl-5-(tributylstanyl)-penta-2,4-dien-1-ol **9a**[31] involved the stannylcupration of enynol **17** with mixed cyanocuprate $Bu_3Sn(Bu)CuCNLi_2$ in THF/Et_2O at −30 °C for 1 h (71% yield).[32]

Transition metal-catalyzed regio- and stereoselective alkyne hydrosilylation reaction was then explored in order to obtain the stereodefined alkenylsilanes, depending upon the substitution pattern of the alkyne. This protocol can be further optimized by judicious changes in the solvent, temperature, the amount of the catalyst and/or the sequence of addition of reagents. Rather than examining different silicon-based reagents (oxygen-activated silanes, "masked silanols") we focused on the C_6 *trans*-benzyldimethylsilylpentadienols as organometallic partners, since they were found to be highly efficient for the synthesis of retinol[17] upon activation by fluoride ions.[33] These derivatives were prepared regio- and stereoselectively by the transition-metal-catalyzed hydrosilylation of the corresponding alkynes.[17] With the exception of the parent system **10a**, the remaining known dienylsilanes previously described have been used as SEM-protected alcohols for the synthesis of protected retinols (9,13-bis-demethyl; 9-demethyl; 13-demethyl; and all-*trans*- and 11-*cis*-isomers),[17] and therefore it would be of interest to evaluate the efficiency of the unprotected dienols in order to expedite the preparation of the methyl-shifted vitamin A analogues.

Alkynylsilane **20** was derived from the treatment of propargylic alcohol **19** with EtMgBr and trapping the alkynyl organomagnesium intermediate with $BnMe_2SiCl$ (87% yield).[34] Alkenylsilane **21a** was obtained by reductive alkyne iodination



Scheme 2 Reagents and reaction conditions: (a) $(Bu_3Sn)_2$, CuCN, *n*-BuLi, THF, −10 °C, overnight, 99%; (b) (i) TBSCl, Et_3N, THF, 97%; (ii) *t*-BuLi, Bu_3SnCl, THF, 77%; (iii) TBAF, THF, 92%; (c) (i) Bu_3SnH, *n*-BuLi, CuCN, MeOH, THF, −78 °C, 30 min; (ii) *p*-TsOH, acetone-H_2O, 80 °C, 45 min, 82%; (d) MnO_2, Na_2CO_3, CH_2Cl_2, 25 °C, 4 h for **13a**, 92%; 4 h for **13b**, 73%; (e) **15a** or **15b**, *n*-BuLi, DMPU, THF, 2 h, −78 °C (**16b**, 94%; **16c**, 73%; **16d**, 70%; **16e**, 70%). (f) Dibal-H, THF, −78 °C, 2–4 h (**9b**, 99%; **9c**, 68%; **9d**, 99%; **9e**, 86%). (g) *n*-Bu_3SnH, CuCN, *n*-BuLi, THF, −30 °C, 45 min (**9a**, 71%).

after reaction of **20** with Red-Al® and trapping the intermediate with molecular iodine. The alkenyliodide intermediate was converted into vinylsilane **21a**[35] upon treatment with MeLi in the presence of CuI (86% overall yield).[36] The aluminate intermediate is considered to be responsible for the selectivity of the carbometallation reaction before being trapped by I_2.[37] Access to alkenylsilane positional isomer **21b** was achieved (in 68% yield) through regio- and stereoselective Cu(I)-catalyzed carbometallation of **20**.[38] (*E*)-3-(benzyldimethylsilyl)prop-2-en-1-ol **21c**[39] was prepared in 72% yield in a single step through the Rh(I)-catalyzed selective hydrosilylation ($[Rh(COD)_2]BF_4$, $BnMe_2SiH$, PPh_3)[39] of propargylic alcohol **19**,[40] by *syn*-addition of Si–H to the alkyne.[41,42] (For the regioselective silylmetallation of 2-butyn-1-ol using a modified procedure, see ref. 43.) Oxidation of the allylic alcohols in alkenylsilanes **21** was carried out uneventfully by treatment with MnO_2 to afford unsaturated aldehydes **22** in 73–90% yield. Only **22b** has been previously described.[44] Unsaturated chain extension by Horner–Wadsworth–Emmons reaction with the corresponding phosphonates **15a** and **15b** as indicated above took place with moderate to good yields (53–89%), despite the low boiling point of these compounds. Final reduction of dienylesters with DIBAL-H at low temperature afforded the silyldienols (**10b–e**; 67–96% yield).

The reported regioselective *cis*-hydrosilylation of enynes to afford (1*E*,3*E*)-dienylsilanes was explored starting from enynols **17** and **25**.[45] Pt-Mediated hydrosilylation[45,46] of enynol **17** [17] after the formation of Karstedt's catalyst [Pt(dvds)(P*t*Bu$_3$)] (dvds = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane) from Pt(DVDS) and P*t*Bu$_3$ (a 1 M solution in toluene) was highly regio- and stereoselective and proceeded as described,[17] to afford **10a** in 69% yield. (For computational studies on the mechanism justifying the regio- and stereoselectivity, see ref. 47.) Following the reported procedure, protected pent-2-en-4-ynol **23**, obtained from **17** (TBDMSCl, imidazole, DMF, 71% yield), was deprotonated with *n*-BuLi, treated with MeI, and the internal alkyne **24** (71% yield) was deprotected with TBAF to afford hex-2-en-4-ynol **25** (94% yield).[31] Pt-mediated hydrosilylation upon reaction of **25** with benzyldimethylsilane in the presence of Karstedt's catalyst at ambient temperature led to isomerically pure internal silane **10f** in 66% yield.

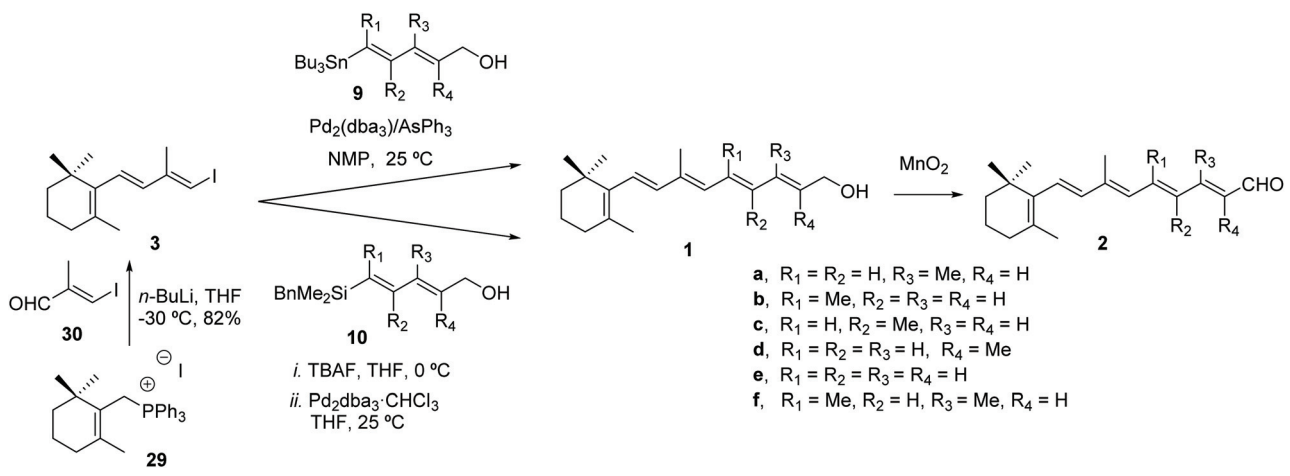
The configuration of the dienols was unambiguously assigned based on the value of the coupling constants (J = 16–20 Hz) in their ^{1}H NMR spectra (*cf.* J = 13–15 Hz for the *Z*-isomers).[41] In addition, nuclear Overhauser effects (nOe) allowed the assignment of the dienylsilane geometries.

As stated above, the dienylsilanes are more stable even upon chromatography purification than the analogous stannanes, although the instability was found to be higher for those lacking the methyl substituent.

The complementary common trienyliodide **3** coupling reagent was prepared in 82% yield by Wittig reaction at moderately low temperatures (−30 °C) of sterically hindered phosphonium salt **29**,[48] and (*E*)-1-iodopropenal **30**. The latter was obtained (86% yield) by oxidation of the corresponding allylic alcohol **14** with MnO_2.[26,49]

For the Pd-catalyzed Stille–Kosugi–Migita cross-coupling of dienylstannanes and trienyliodides, the procedure already optimized[50] using the conditions of Scheme 4 ($Pd_2(dba)_3$, $AsPh_3$, NMP, 25 °C)[51] was adopted, which uneventfully provided the corresponding all-*trans*-retinol **1a** and analogues **1b–f** in the yields shown in Table 1.

For the Hiyama–Denmark cross-coupling,[17] activation of the silane by a base[12,52] was required to form the pentacoordinated species, and TBAF was selected among the various sources of fluoride ions.[33,53] Following the protocol already optimized for all-*trans*-retinol **1a**[16,17] using $Pd_2dba_3{\cdot}CHCl_3$ as the catalyst and nBu$_4$NF as the organosilane activator, the coupling of **10a–f** and trienyliodide **3** proceeded at ambient temperature in yields (39–86%) that are dependent upon the substitution pattern of the diene (Table 1). Side-by-side comparison with the Stille–Kosugi–Migita cross-coupling for the same components confirms that the Hiyama–Denmark cross-coupling proceeded affording higher yields and is therefore more efficient for the synthesis of these unstable polyenes.

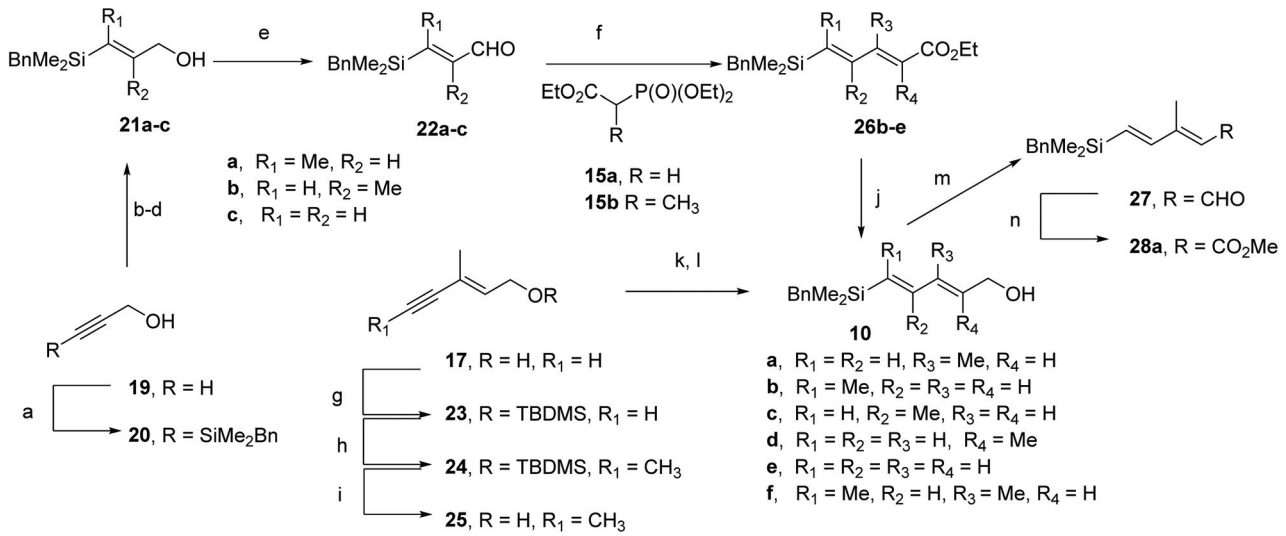


Scheme 4 Stille–Kosugi–Migita and Hiyama–Denmark cross-coupling reaction for the synthesis of C11 to C14-methyl shifted retinoids.

Table 1 Yields (%) for the Hiyama–Denmark and Stille–Kosugi–Migita cross-coupling reactions to provide vitamin A and analogues, and allylic oxidation to the corresponding retinals (Scheme 4)

No.	R_1, R_2, R_3, R_4	Yield (%) Hiyama–Denmark	Yield (%) Stille–Kosugi–Migita	Yield (%) Oxidation
1	H, H, Me, H	**1a**, 82	**1a**, 60	**2a**, 76
2	Me, H, H, H	**1b**, 41	**1b**, 37	**2b**, 88
3	H, Me, H, H	**1c**, 67	**1c**, 44	**2c**, 76
4	H, H, H, Me	**1d**, 62	**1d**, 22	**2d**, 82
5	H, H, H, H	**1e**, 86	**1e**, 31	**2e**, 60
6	Me, H, Me, H	**1f**, 41	N.T.	**2f**, 65

N.T.: not tested.



Scheme 3 Reagents and reaction conditions: (a) EtMgBr (2.7 mol equiv.), $BnMe_2SiCl$ (2.7 mol equiv.), THF, 70 °C, 2 h, 87%; (b) (i) **20**, Red-Al®, I_2, Et_2O, 25 °C, 2 h; (ii) MeLi, CuI, Et_2O, −20 °C, 20 h; **21a**, 86%; (c) **20**, MeMgCl (6.76 mol equiv.), CuI (cat), Et_2O, 40 °C, 21 h; **21b**, 68%; (d) **19**, $HSiMe_2Bn$, $[Rh(COD)_2]BF_4$ (5% mol), PPh_3, acetone, 25 °C, 15 h; **21c**, 72%; (e) MnO_2, Na_2CO_3, CH_2Cl_2, 25 °C, 2–4 h (**22a**, 73%; **22b**, 73%; **22c**, 90%); (f) **15a** or **15b**, *n*BuLi, DMPU, THF, −78 °C, 2.5 h (**26b**, 56%; **26c**, 89%; **26d**, 61%; **26e**, 53%). (g) TBDMSCl, imidazole, DMF, overnight, 25 °C, 91%; (h) *n*-BuLi, MeI, THF, 1.5 h, −30 °C, 71%; (i) TBAF, THF, 0.5 h, 25 °C, 94%; (j) Dibal-H, THF, −78 °C, 2 h (**10b**, 75%; **10c**, 82%; **10d**, 67%; **10e**, 96%); (k) $HSiMe_2Bn$ (2.5 mol equiv.), Pt(DVDS) (5 mol%), tBu_3P (5 mol%), THF, 2 h (**10a**, 69%); (l) (i) $HSiMe_2Bn$ (1.5 mol equiv.), Pt(DVDS) (5 mol%), tBu_3P (5 mol%), THF, 25 °C, 0.5 h; (ii) alkyne **17** (1 equiv.), THF, 25 °C, 2.5 h (**10f**, 66%); (m) MnO_2, Et_2O, 25 °C, 1.5 h, 90%; and (n) MnO_2, KCN, MeOH, 25 °C, 2 h, 65%.

Silyldienyl esters **26** (Scheme 3) were also tested in Hiyama–Denmark cross-coupling with trienyliodide **3**, but extensive protodesilylation was observed and the corresponding terminal dienoates were obtained as the main products, regardless of the nature of the activation reagent and activation times (see the ESI†).[54] Likewise, silyldienals are not appropriate substrates for the Hiyama–Denmark cross-coupling.[11–13] In contrast, both stannyldienals and stannyldienyl esters efficiently provide retinal analogs and methyl esters of retinoic acids upon Stille cross-coupling, although some isomerization was noted for the former (see the ESI†).

These compounds with pentadiene-1-ol substructures, namely all-*trans*-retinol **1a**, all-*trans*-13-demethyl-11-methylretinol **1b**, all-*trans*-13-demethyl-12-methylretinol **1c**,[55] all-*trans*-13-demethyl-14-methylretinol **1d**,[56] all-*trans*-13-demethylretinol **1e**[56] and all-*trans*-11-methylretinol **1f**, were uneventfully oxidized upon treatment with MnO_2 to afford the series of retinals **2a–f**, namely all-*trans*-retinal **2a**,[16,57] all-*trans*-13-demethyl-11-methylretinal **2b**, all-*trans*-13-demethyl-12-methylretinal **2c**,[55] all-*trans*-13-demethyl-14-methylretinal **2d**,[55] all-*trans*-13-demethylretinal **2e**,[56,58] and all-*trans*-11-methylretinal **2f**, in good to excellent yields (60–88%, Table 1).

Biological evaluation

The synthetic all-*trans*-retinal analogues (with the exception of the highly unstable **2e**) were characterized as substrates of human AKR1B1 and AKR1B10 enzymes. The determination of the kinetic parameters K_m, k_{cat} and k_{cat}/K_m (summarized in

Table 2 Kinetic parameters of human AKR1B enzymes for C11 to C14-methyl shifted retinal analogues **2a–f**[a]

	K_m (μM)		k_{cat} (min^{-1})		k_{cat}/K_m (mM^{-1} min^{-1})	
Compound	AKR1B1	AKR1B10	AKR1B1	AKR1B10	AKR1B1	AKR1B10
2b	1.2 ± 0.4	8.5 ± 1.8	20 ± 1	72 ± 7	16 400 ± 4900	8500 ± 2000
2c	2.9 ± 0.8	12 ± 2	15 ± 1	19 ± 1	5100 ± 1500	1700 ± 300
2d	0.9 ± 0.2	1.8 ± 0.3	1.6 ± 0.1	1.5 ± 0.1	1700 ± 300	800 ± 100
2f	2.8 ± 0.6	0.8 ± 0.2	5.5 ± 0.4	80 ± 4	2000 ± 500	106 000 ± 23 200
All-*trans*-retinal **2a**[b]	1.1 ± 0.1	0.6 ± 0.1	0.9 ± 0.1	27 ± 1	1300 ± 200	45 000 ± 7600

[a] Values of the kinetic parameters (and standard errors) were calculated by fitting the data to the Michaelis–Menten curve using GraFit 5.0 (Eritacus software). [b] Data taken from ref. 59.

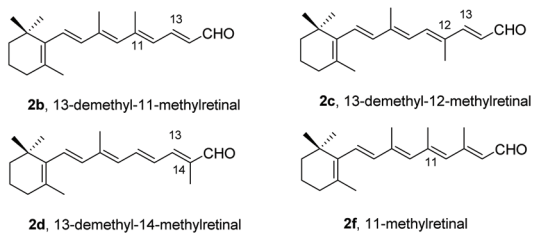


Fig. 1 Structures of C11-to-C14 methyl-shifted all-*trans*-retinal analogues tested as substrates of AKR1B1 and AKR1B10.

Table 2) allowed the study of the different specificities of these enzymes for the tested compounds, which could be useful in elucidating catalytic mechanisms that are not yet fully understood, and also in identifying structures that could serve as the basis for the design of AKR inhibitors of pharmacological interest.

The K_m values for AKR1B1 of the four retinal analogues examined (Fig. 1) are very similar to that of the parent all-*trans*-retinal **2a**, in the micromolar range. Regarding the catalytic constant (k_{cat}), all analogues exhibited a higher value than the parent compound. In particular, compounds **2b** and **2c** were found to be the most active, and displayed the highest catalytic efficiency (k_{cat}/K_m, the constant that better measures the specificity for the substrate) values. This indicates that the location of the methyl groups in these compounds is the most favorable for catalysis.

Regarding AKR1B10, all compounds exhibited higher K_m values than the parent all-*trans*-retinal **2a**, in particular compounds **2b** and **2c**, indicating that the positional changes of the methyl group in these analogues may partially impair substrate binding. In terms of k_{cat}, the high values of the C11-methyl analogues **2b** and **2f** are noticeable, which might suggest that the methyl group at C-11 somehow assists in the catalysis. When the catalytic efficiencies are compared, it is remarkable that all analogues exhibited a lower value than the parent compound with the exception of **2f**, which showed the highest value measured for any retinoid with AKR1B10. This compound is the only analogue endowed with an additional methyl group at the polyunsaturated chain, being therefore the most hydrophobic and also the compound with the highest inductive (electron-donating) effect by methyl substituents. This structural (steric/electronic) feature on the substrate appears to favor its efficient enzymatic reduction. The Michaelis–Menten kinetics of both AKR1B1 and AKR1B10 with compound **2f** are shown in Fig. 2.

AKR1B10 is the only reported AKR1B enzyme with a high k_{cat} value for the reduction of all-*trans*-retinal **2a** to all-*trans*-retinol **1a**.[60] Its specificity for all-*trans*-retinal **2a** might be related to the lysine residue at position 125 (which is a leucine residue in AKR1B1).[61] This was supported by testing the enzy-

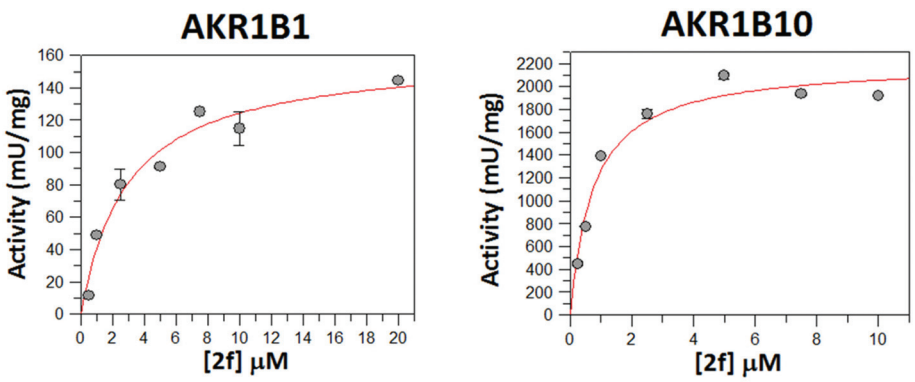


Fig. 2 Representative Michaelis–Menten kinetics of AKR1B1 and AKR1B10 with compound **2f**. The reaction was carried out in 100 mM sodium phosphate, pH 7.2, at 37 °C. The initial rates were measured with at least seven different substrate concentrations. Experimental values were adjusted to the Michaelis–Menten equation using the non-linear regression program GraFit 5.0 (Eritacus software).

matic activity of AKR1B1 and AKR1B10 with ring-oxidized retinal derivatives (those containing hydrophilic groups at the cyclohexenyl ring C4 position) as substrates. These compounds exhibited much larger k_{cat} values compared to all-*trans*-retinal **2a** in the case of AKR1B1, but no significant differences were observed with AKR1B10. Additional studies,[22] centered on the effects caused by the presence of a methyl group on the cyclohexene ring, indicated a net decrease in the k_{cat} value with both enzymes. In the present study, by changing the location of the methyl group at C13 to the C11–C14 positions of the unsaturated side chain, higher k_{cat} values were obtained in AKR1B1 with retinal analogues, significantly improved with respect to the already reported values for AKR1B10 with all-*trans*-retinal **2a**.

Previous studies[18,59,62,63] have pointed out the importance of the hydrophobic amino acid residues lining the substrate-binding pocket of AKR1B enzymes in modulating the interaction with all-*trans*-retinal **2a**: Trp20 (AKR1B1 numbering)/Trp21 (AKR1B10 numbering), Val47/Val48, Trp79/Trp80, Trp111/Trp112, Phe115/Phe116, Phe122/Phe123, Leu124 in AKR1B1, Trp219/Trp220, Cys298/Cys299, and Leu300/Val301. Specifically, for AKR1B1, it was predicted that Leu124 interacts with the cyclohexene ring of all-*trans*-retinal **2a**, Leu300 with the methyl group at C9, and Trp111 with the C12 atom, and all must contribute to a slower product release and thus a lower k_{cat} value for this enzyme as compared to AKR1B10. Based on the molecular models of all-*trans*-retinal **2a** docked to AKR1B enzymes,[18,59] we may now postulate the following structure–function relationships for the compounds **2b–f** analyzed here.

Compounds **2b** and **2f** have in common the presence of a methyl group at C11 and, interestingly, they display high k_{cat} values for both AKR1B1 and AKR1B10. We hypothesize that this methyl group, located in the middle section of the polyene chain, could provide an unfavorable environment or steric hindrance with nearby amino acid residues of the substrate-binding pocket, which in this case would favor a faster release of the reaction product. According to previous observations,[59] if product dissociation were the rate-limiting step, this would explain the observed high k_{cat} values. The situation is reminiscent of the results obtained when four Phe residues (including Phe48) were introduced in the substrate-binding pocket of AKR1B10.[62] There the resulting mutant enzyme displayed one of the highest k_{cat} values (75 min^{-1}) with all-*trans*-retinal **2a**, resembling the values obtained here with compounds **2b** and **2f** (72 and 80 min^{-1}, respectively). This finding strongly supports the hypothesis that the presence of a methyl group at C11 of the retinal substrate or a close hydrophobic residue in the substrate-binding pocket may favor the product release in both AKR1B1 and AKR1B10. As for compound **2c** with a methyl group at C12, it may have an opposing effect in AKR1B1 or AKR1B10. In AKR1B1, C12 is predicted to bind close to Trp111[18] and thus the presence of the extra methyl group at C12 may again impair a proper interaction with AKR1B1, resulting in a higher k_{cat} value. Conversely, the methyl group may interact with the open conformation of Trp112 in AKR1B10, leading to a slower release and a lower k_{cat} value. Finally, compound **2d** is the worst substrate in terms of k_{cat}. The close proximity of the methyl group at C14 to the carbonyl group and active-site catalytic residues may cause a steric hindrance, thus preventing a correct substrate orientation for a productive catalysis.

Conclusions

Side-by-side comparison of the Stille–Kosugi–Migita and Hiyama–Denmark cross-coupling reactions for the synthesis of vitamin A analogues allowed the confirmation of previous results on the parent system,[17] favoring the latter protocol for the synthesis of these pentaenes. The Hiyama–Denmark cross-coupling of unsaturated silicon reagents offers the advantages of the greater stability (and lower toxicity) of the dienylsilanes due to the low polarizability of the C–Si bond, the straightforward preparation of substituted dienes, the mild reaction conditions and the high yields. As a general trend, yields were lower when the methyl substituent of the diene is placed geminal to the silane (**1c** and **1f**), which may be taken as an indication of the steric hindrance of the pentavalent silicon intermediate to undergo efficient cross-coupling reactions. This limitation is shared by the Stille–Kosugi–Migita and Suzuki–Miyaura cross-coupling reactions for the synthesis of substituted polyenes, such as the retinoids, since they are sensitive to the steric bulkiness of the components.[3]

The availability of methyl-shifted retinoids, by changing the location of the methyl group at C13 to the C11–C14 positions of the unsaturated side chain, has allowed scanning the topology of the substrate-binding pocket of AKR1B enzymes. Regarding the kinetic properties, compounds **2b** and **2f** were found to be the best substrates for AKR1B1 and AKR1B10, respectively. Importantly, both enzymes displayed a higher catalytic efficiency with these compounds than with the previously reported substrates all-*trans*-retinal **2a** (and also 9-*cis*-retinal, not shown)[59] and ring-substituted derivatives.[22] This is particularly remarkable in the case of AKR1B10, for which the catalytic efficiency exhibited with all-*trans*-retinal **2a** could not be previously improved with synthetic retinoids as substrates. Nevertheless, further studies are required in order to determine the mechanism(s) underlying these high substrate specificities.

In summary, these results appear to be very promising in order to develop novel compounds with better pharmacophores by using structure-based drug design. The importance of the hydrophobic interactions, between the methyl groups at the C11–C14 positions of the substrate and the amino acid residues lining the enzyme binding pocket, has been unveiled as they are important for substrate binding and may play a role in inhibitor efficacy. The present studies could lead to a better understanding of the AKR structure and function, and could pave the way for the development of new inhibitor compounds for the treatment of diseases such as diabetes or cancer.

Experimental section

General experimental procedures

See the ESI.†

Ethyl (2*E*–4*E*)-4-methyl-5-(tributylstannyl)penta-2,4-dienoate 16c

General procedure for the Horner–Wadsworth–Emmons reaction. To a cooled (0 °C) solution of triethyl-2-methyl-phosphonoacetate **15a** (0.52 mL, 2.34 mmol) in THF (2.7 mL), *n*-BuLi (0.063 mL, 1.6 M in hexanes, 0.98 mmol) and DMPU (0.15 mL, 1.2 mmol) were added and the reaction mixture was stirred for 1 h at 0 °C. The temperature was cooled down to −78 °C and a solution of aldehyde **13b**[25] (0.16 g, 0.446 mmol) in THF (2 mL) was then added. After stirring for 2 h, water was added and the resulting mixture was extracted with Et_2O (3×). The combined organic layers were washed with H_2O (3×), brine (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 97 : 3 hexane/EtOAc) to afford 0.14 g (73%) of a yellow oil, which was identified as **16c**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.68 (d, J = 15.7 Hz, H_3), 6.37 (s, J_{Sn-H} = 30.2 Hz, H_5), 5.91 (d, J = 15.7 Hz, H_2), 4.10 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 1.77 (s, 3H, C_4–CH_3), 1.52 (m, 6H, Sn–nBu_3), 1.33 (m, 6H, Sn–nBu_3), 1.03 (td, J = 7.1, 1.9 Hz, 3H, OCH_2CH_3), 0.98–0.89 (m, 15H, Sn–nBu_3) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 167.0 (s), 149.5 (s), 148.9 (d), 144.5 (d), 117.3 (d), 60.2 (t), 29.6 (t, 3×, J_{Sn-C} = 9.9 Hz), 27.7 (t, 3×, J_{Sn-C} = 25.9 Hz), 20.4 (q), 14.5 (q), 13.9 (q, 3×), 10.5 (t, 3×, J_{Sn-C} = 162 Hz) ppm. **UV** (MeOH): λ_{max} 277, 254 nm. **IR** (NaCl): ν 2957 (m, C–H), 1716 (s, C=O), 1171 (s, C–O), 871 (s) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 431 (100, $[M + H]^+$), 429 (75), 427 (43), 332 (26). **HRMS** (ESI$^+$): calcd for $C_{20}H_{39}O_2Sn$ ($[M + H]^+$), 431.1979; found, 431.1967.

(2*E*,4*E*)-5-(tri-*n*-Butylstannyl)-4-methylpenta-2,4-dien-1-ol 9c

General procedure for Dibal-H reduction of esters. To a cooled (−78 °C) solution of ethyl (2*E*,4*E*)-4-methyl-5-(tributylstannyl) penta-2-,4-dienoate **16c** (0.1 g, 0.23 mmol) in THF (1.2 mL), DIBAL-H (0.59 mL, 1 M in THF, 0.59 mmol) was added. After stirring at −78 °C for 2 h, water was added. The resulting mixture was extracted with EtOAc (3×), the organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 80 : 15 : 5 hexane/EtOAc/Et_3N) to afford 61 mg (68%) of a yellow oil, which was identified as **9c**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 6.36 (d, J = 16.2 Hz, H_3), 6.07 (s, J_{Sn-H} = 33.7 Hz, H_5), 5.58 (dt, J = 16.2, 5.6 Hz, H_2), 1.93 (s, 3H, C_4–CH_3), 1.66–1.57 (m, 6H, Sn–nBu_3), 1.39 (dt, J = 14.7, 7.3 Hz, 6H, Sn–nBu_3), 1.06–1.00 (m, 6H, Sn–nBu_3), 0.94 (t, J = 7.3 Hz, 9H, Sn–nBu_3) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 150.7 (s), 136.4 (d, J_{Sn-C} = 45.3 Hz), 132.8 (d), 127.9 (d), 63.4 (t), 29.7 (t, 3×), 27.7 (t, 3×, J_{Sn-C} = 38.7 Hz), 21.1 (q), 14.0 (q, 3×), 10.6 (t, 3×) ppm. **IR** (NaCl): ν 3550–3100 (br, O–H), 2956 (m, C–H), 2870 (m, C–H), 1568 (m), 1459 (m), 965 (s) cm^{-1}. **HRMS** (ESI$^+$): calcd for $C_{12}H_{27}Sn$ ($[M + H]^+$), 291.1140; found, 291.1129.

Ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)-5-methylpenta-2,4-dienoate 26b

General procedure for MnO_2 oxidation of allylic alcohols. To a cooled (0 °C) solution of (*E*)-3-(benzyldimethylsilyl)-3-methyl-prop-2-en-1-ol **21a** (0.094 g, 0.43 mmol) in CH_2Cl_2 (17 mL), MnO_2 (0.67 g, 7.68 mmol) and Na_2CO_3 (0.82 g, 7.68 mmol) were added and the resulting mixture was stirred at 25 °C for 2.5 h. The mixture was filtered through Celite® and washed with CH_2Cl_2, and the solvent was evaporated to afford 90.9 mg (73%) of a yellow oil, which was used in the next step without further purification.

Following the general procedure for the Horner–Wadsworth–Emmons reaction, the reaction of the residue obtained above (0.091 g, 0.42 mmol), triethyl-phosphonoacetate **15a** (0.12 mL, 0.11 g, 1.0 mmol), *n*-BuLi (0.37 mL, 2.45 M in hexanes, 0.92 mmol) and DMPU (0.135 mL, 1.12 mmol) in THF (4.17 mL) afforded, after purification by flash-column chromatography (silica gel, 98 : 2 hexane/EtOAc), 70 mg (56%) of a yellow oil, which was identified as **26b**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.95 (dd, J = 16.0, 10.7 Hz, 1H, H_3), 7.12 (t, J = 7.5 Hz, 2H, ArH), 6.99 (t, J = 7.4 Hz, 1H, ArH), 6.87 (d, J = 7.1 Hz, 2H, ArH), 6.32 (d, J = 10.7 Hz, 1H, H_4), 5.96 (d, J = 15.2 Hz, 1H, H_2), 4.09 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 1.95 (s, 2H, $SiMe_2CH_2Ph$), 1.59 (d, J = 1.6 Hz, 3H, C_5–CH_3), 1.01 (t, J = 7.1 Hz, 3H, OCH_2CH_3), −0.08 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 167.0 (s), 149.2 (s), 139.7 (s), 138.7 (d), 135.8 (d), 128.6 (d, 2×), 128.5 (d, 2×), 124.7 (d), 122.6 (d), 60.2 (t), 24.8 (t), 16.0 (q), 14.4 (q), −4.4 (q, 2×) ppm. **IR** (NaCl): ν 2957 (m, C–H), 1713 (s, C=O), 1621 (m), 1269 (s, C–O), 830 (s) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 289 (22, $[M + H]^+$), 197 (100), 175 (57). **HRMS** (ESI$^+$): calcd for $C_{17}H_{25}O_2Si$ ($[M + H]^+$), 289.1618; found, 289.1615.

Ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)-4-methylpenta-2,4-dienoate 26c. Following the general procedure for the Horner–Wadsworth–Emmons reaction, the reaction of (*E*)-3-(benzyldimethylsilyl)-2-methylacrylaldehyde **22b** (0.16 g, 0.818 mmol), triethyl-2-methyl-phosphonoacetate **15b** (0.22 mL, 0.21 g, 1.07 mmol), *n*-BuLi (0.6 mL, 1.8 M in hexanes, 1.06 mmol) and DMPU (0.3 mL, 2.20 mmol) in THF (8.2 mL) afforded, after purification by flash-column chromatography (silica gel, 98 : 2 hexane/EtOAc), 0.21 g (89%) of a yellow oil, which was identified as **26c**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.54 (d, J = 16.6 Hz, 1H, H_3), 7.04–6.96 (m, 2H, ArH), 6.95–6.86 (m, 1H, ArH), 6.90–6.86 (d, J = 7.2 Hz, 2H, ArH), 5.93 (d, J = 15.8 Hz, 1H, H_2), 5.70 (s, 1H, H_5), 4.09 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 1.99 (s, 2H, $SiMe_2CH_2Ph$), 1.53 (s, 3H, C_4–CH_3), 1.02 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.00 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 166.8 (s), 150.1 (d), 149.2 (s), 139.7 (s), 139.6 (d), 128.6 (d, 2×), 128.5 (d, 2×), 124.7 (d), 118.5 (d), 60.3 (t), 26.3 (t), 17.4 (q), 14.4 (q), −2.2 (q, 2×) ppm. **UV** (MeOH): λ_{max} 266 nm. **IR** (NaCl): ν 2955 (m, C–H), 1713 (s, C=O), 1159 (s, C–O), 836 (s) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 290 (21), 289 (100, $[M + H]^+$), 139 (14). **HRMS** (ESI$^+$): calcd for $C_{17}H_{25}O_2Si$ ($[M + H]^+$), 289.1618; found, 289.1624.

Ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)penta-2-methylpenta-2,4-dienoate 26d. Following the general procedure for the Horner–Wadsworth–Emmons reaction, the reaction of (*E*)-(benzyldimethylsilyl)-propenal **22c** (0.20 g, 0.98 mmol), triethyl-2-methyl-phosphonoacetate **15b** (0.52 mL, 2.34 mmol), *n*-BuLi (0.88 mL, 2.45 M in hexanes, 2.15 mmol) and DMPU

(0.37 mL, 2.64 mmol) in THF (9.8 mL) afforded, after purification by flash-column chromatography (silica gel, 98 : 2 hexane/EtOAc), 0.17 g (61%) of a yellow oil, which was identified as **26d**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.41 (d, J = 13.3 Hz, 1H, H_3), 7.17–7.11 (m, 2H, ArH), 7.05–6.97 (m, 1H, ArH), 6.97–6.88 (m, 2H, ArH), 6.79 (dd, J = 18.3, 10.9 Hz, 1H, H_4), 6.06 (d, J = 18.5 Hz, 1H, H_5), 4.06 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.00 (s, 2H, $SiMe_2CH_2Ph$), 1.94 (s, 3H, C_2–CH_3), 1.00 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.00 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 168.0 (s), 140.8 (d), 140.3 (d), 139.9 (d), 139.6 (s), 128.6 (d, 4×), 124.7 (d), 60.6 (t), 25.9 (t), 14.4 (q), 13.0 (q), −3.5 (q, 2×) ppm. **IR** (NaCl): ν 2980 (m, C–H), 2956 (m, C–H), 2316 (w), 1706 (s, C═O), 1272 (m), 1208 (C–O), 835 (s) cm^{-1}. **UV** (MeOH): λ_{max} 268, 222 nm. **MS** (ESI$^+$-TOF): m/z (%) 289 (100, $[M + H]^+$), 271 (13), 254 (1). **HRMS** (ESI$^+$): calcd for $C_{17}H_{25}O_2Si$ ($[M + H]^+$), 289.1618; found, 289.1623.

Ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)penta-2,4-dienoate 26e. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of (*E*)-3-(benzyldimethylsilyl)prop-2-en-1-ol **21c** (0.25 g, 1.21 mmol), MnO_2 (1.9 g, 21.8 mmol) and Na_2CO_3 (2.31 g, 21.8 mmol) in CH_2Cl_2 (48.46 mL) for 2 h at 25 °C, afforded 0.22 g (90%) of a yellow oil, which was used in the next step without further purification.

Following the general procedure for the Horner–Wadsworth–Emmons reaction, the reaction of the residue obtained above (0.22 g, 1.09 mmol), triethylphosphonoacetate **15a** (0.52 mL, 2.61 mmol), *n*-BuLi (0.98 mL, 2.45 M in hexanes, 2.39 mmol) and DMPU (0.35 mL, 2.93 mmol) in THF (10.87 mL) afforded, after purification by flash-column chromatography (silica gel, 98 : 2 hexane/EtOAc), 0.17 g (53%) of a yellow oil, which was identified as **26e**. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 7.42 (dd, J = 15.4, 10.5 Hz, 1H, H_3), 7.18–7.10 (m, 2H, ArH), 7.12 (t, J = 7.3 Hz, 1H, ArH), 7.01 (d, J = 7.3 Hz, 2H, ArH), 6.89 (dd, J = 18.4, 10.5 Hz, 1H, H_4), 6.39 (d, J = 18.4 Hz, 1H, H_5), 5.92 (d, J = 16.8 Hz, 1H, H_2), 4.05 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 1.94 (s, 2H, $SiMe_2CH_2Ph$), 0.99 (t, J = 7.1 Hz, 3H, OCH_2CH_3), −0.07 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 166.5 (s), 146.1 (d), 142.8 (d), 142.3 (d), 139.5 (s), 128.6 (d, 2×), 128.5 (d, 2×), 124.7 (d), 122.7 (d), 60.3 (t), 25.7 (t), 14.4 (q), −3.7 (q, 2×) ppm. **IR** (NaCl): ν 2956 (m, C–H), 1714 (s, C═O), 1219 (s), 835 (s) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 275 (100, $[M + H]^+$), 197 (42), 192 (44), 175 (97), 63 (32). **HRMS** (ESI$^+$): calcd for $C_{16}H_{23}O_2Si$ ($[M + H]^+$), 275.1462; found, 275.1464.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)-3-methylpenta-2,4-dienal 27. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of (2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-ol **10a** (2.3 g, 9.33 mmol) and MnO_2 (8.11 g, 93.34 mmol) in Et_2O (373 mL) for 1.5 h at 25 °C afforded 2.05 g (90%) of a yellow oil, which was identified as **27**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 9.96 (d, J = 7.8 Hz, 1H, H_1), 7.19–7.13 (m, 2H, ArH), 7.03 (t, J = 7.4 Hz, 1H, ArH), 6.92 (d, J = 8.2 Hz, 2H, ArH), 6.39 (d, J = 19.0 Hz, 1H, H_5), 6.15 (d, J = 19.0 Hz, 1H, H_4), 5.85 (d, J = 8.3 Hz, 1H, H_2), 2.00 (s, 2H, $SiMe_2CH_2Ph$), 1.65 (s, 3H, C_3–CH_3), −0.01 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 190.7 (d), 152.9 (s), 147.8 (d), 139.5 (s), 135.9 (d), 130.8 (d), 128.6 (d, 2×), 128.5 (d, 2×), 124.8 (d), 25.8 (t), 12.0 (q), −3.6 (q, 2×) ppm. **UV** (MeOH): λ_{max} 274, 222 nm. **IR** (NaCl): 2956 (w, C–H), 1663 (s, C═O), 1204 (m), 839 (s) cm^{-1}. **HRMS** (ESI$^+$): calcd for $C_{15}H_{21}OSi$ ($[M + H]^+$), 245.1356; found, 245.1355.

Methyl (2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dienoate 28a. To a cooled (0 °C) solution of methyl (2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dienal **27** (0.33 g, 1.36 mmol) in methanol (7 mL), MnO_2 (2.24 g, 25.56 mmol) and KCN (0.45 g, 70.53 mmol) were added and the reaction mixture was stirred at 25 °C for 2 h. The mixture was filtered through Celite®, and was washed with CH_2Cl_2. The solution was washed with an saturated aqueous solution of NaCl (3×), dried (Na_2SO_4) and the solvent was evaporated to afford 0.24 g (65%) of a yellow oil, which was identified as **28a**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.21–7.10 (m, 2H, ArH), 7.02 (t, J = 7.4 Hz, 1H, ArH), 6.92 (d, J = 7.1 Hz, 1H, ArH), 6.44 (d, J = 19.0 Hz, 1H, H_4 or H_5), 6.15 (d, J = 18.9 Hz, 1H, H_5 or H_4), 5.88 (s, 1H, H_2), 3.42 (s, 3H, OCH_3), 2.33 (s, 2H, $SiMe_2CH_2Ph$), 1.99 (s, 3H, CH_3), −0.01 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 167.2 (s), 152.7 (s), 148.1 (d), 139.7 (s), 134.3 (d), 128.6 (d, 2×), 128.5 (d, 2×), 124.7 (d), 120.8 (d), 50.8 (q), 25.9 (t), 13.4 (q), −3.5 (q) ppm. **UV** (MeOH): λ_{max} 265, 222 nm. **IR** (NaCl): ν 2953 (m, C–H), 1717 (w, C═O), 1156 (s, C–O), 838 (s) cm^{-1}. **HRMS** (ESI$^+$): calcd for $C_{16}H_{23}O_2Si$ ($[M + H]^+$) 275.1462; found 275.1461.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)-5-methylpenta-2,4-dien-1-ol 10b. Following the general procedure for Dibal-H reduction of esters, the reaction of ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)-5-methylpenta-2,4-dienoate **26b** (0.07 g, 0.24 mmol) and DIBAL-H (0.61 mL, 1 M in THF, 0.61 mmol) in THF (1.2 mL) for 2 h at −78 °C afforded, after purification by flash-column chromatography (silica gel, 90 : 10 hexane/EtOAc), 44.7 mg (75%) of a yellow oil, which was identified as **10b**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.16–7.12 (m, 2H, ArH), 6.96 (t, J = 7.7 Hz, 1H, ArH), 6.65–6.54 (m, 2H, ArH), 6.60 (dd, J = 15.1, 10.7 Hz, 1H, H_3), 6.37 (d, J = 12.0 Hz, 1H, H_4), 5.63 (dt, J = 15.1, 5.5 Hz, 1H, H_2), 3.92–3.81 (m, 2H, $2H_1$), 2.07 (s, 2H, $SiMe_2CH_2Ph$), 1.72 (s, 3H, C_5–CH_3), 0.04 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 140.3 (s), 138.1 (d), 137.3 (s), 134.3 (d), 128.5 (d, 4×), 126.1 (d), 124.5 (d), 63.2 (t), 25.2 (t), 15.5 (q), −4.1 (q, 2×) ppm. **IR** (NaCl): ν 3500–3100 (br, O–H), 2954 (m, C–H), 2920 (m, C–H), 1599 (m), 1493 (m), 830 (s) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 271 ($[M + Na]^+$, 5), 229 (12), 213 (18), 197 (100). **HRMS** (ESI$^+$): calcd for $C_{15}H_{23}OSi$ ($[M + H]^+$) 247.1513; found, 247.1519.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)-4-methylpenta-2,4-dien-1-ol 10c. Following the general procedure for Dibal-H reduction of esters, the reaction of ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)-4-methylpenta-2,4-dienoate **26c** (0.09 g, 0.34 mmol) and DIBAL-H (0.85 mL, 1 M in THF, 0.85 mmol) in THF (1.8 mL) for 2 h at −78 °C afforded, after purification by flash-column chromatography (silica gel, 90 : 10 hexane/EtOAc), 0.07 g (82%) of a yellow oil, which was identified as **10c**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.16–7.12 (m, 3H, ArH), 7.05–6.96 (m, 2H, ArH), 6.22 (d, J = 16.5 Hz, H_3), 5.63–5.53 (dt, J = 15.7, 5.5

Hz, H_2), 5.52 (s, H_5), 3.87 (d, J = 5.5 Hz, H_1), 2.12 (s, 2H, $SiMe_2CH_2Ph$), 1.72 (s, 3H, C_4–CH_3), 0.12 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 150.8 (s), 140.3 (s), 137.0 (d), 129.7 (d), 129.2 (d), 128.6 (d, 4×), 127.8 (d), 63.2 (t), 26.8 (t), 18.1 (q), −1.7 (q, 2×) ppm. **UV** (MeOH): λ_{max} 245 nm. **IR** (NaCl): ν 3550–3100 (br, O–H), 2951 (m, C–H), 2917 (m, C–H), 1579 (m), 1493 (m), 854 (s) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 248 (19), 247 (100, $[M + H]^+$), 230 (5), 229 (26). **HRMS** (ESI$^+$): calcd for $C_{15}H_{23}OSi$ ($[M + H]^+$), 247.1513; found, 247.1513.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)-2-methylpenta-2,4-dien-1-ol 10d. Following the general procedure for Dibal-H reduction of esters, the reaction of ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl) penta-2-methylpenta-2,4-dienoate **26d** (0.28 g, 0.97 mmol) and DIBAL-H (2.4 mL, 1 M in THF, 2.4 mmol) in THF (4.9 mL) for 2 h at −78 °C afforded, after purification by flash-column chromatography (silica gel, 90 : 10 hexane/EtOAc), 0.16 g (67%) of a yellow oil, which was identified as **10d**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 7.20–7.12 (m, 3H, ArH), 7.05–6.97 (m, 2H, ArH), 6.86 (dd, J = 18.3, 10.5 Hz, 1H, H_4), 6.11 (d, J = 12.8 Hz, 1H, H_3), 5.86 (d, J = 18.3 Hz, 1H, H_5), 3.70 (d, J = 5.6 Hz, 2H, $2H_1$), 2.10 (s, 2H, $SiMe_2CH_2Ph$), 1.56 (s, 3H, C_2–CH_3), 0.09 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 141.3 (d), 140.2 (s), 139.0 (s), 131.3 (d), 128.6 (d, 2×), 128.5 (d, 2×), 127.6 (d), 124.5 (d), 67.9 (t), 26.4 (t), 14.2 (q), −3.1 (q, 2×) ppm. **IR** (NaCl): ν 3500–3060 (br, O–H), 2953 (m, C–H), 1490 (m), 1248 (m), 1156 (s), 858 (s), 830 (s) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 247 ($[M + H]^+$, 43), 229 (100), 227 (43), 223 (10), 189 (80). **HRMS** (ESI$^+$): calcd for $C_{15}H_{21}OSi$ ($[M + H]^+$), 245.1356; found, 245.1356.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)penta-2,4-dien-1-ol 10e. Following the general procedure for Dibal-H reduction of esters, the reaction of ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)penta-2,4-dienoate **26e** (0.17 g, 0.61 mmol) and DIBAL-H (1.51 mL, 1 M in THF, 1.51 mmol) in THF (3 mL) for 3 h at −78 °C afforded, after purification by flash-column chromatography (silica gel, 90 : 10 hexane/EtOAc), 0.14 g (96%) of a yellow oil, which was identified as **10e**. **^{1}H NMR** (400.13 MHz, C_6D_6): δ 7.21–7.10 (m, 2H, ArH), 7.07–6.92 (m, 3H, ArH), 6.52 (dd, J = 18.4, 10.1 Hz, 1H, H_4), 6.16 (dd, J = 15.7, 10.4 Hz, 1H, H_3), 5.78 (d, J = 18.4 Hz, 1H, H_5), 5.58 (dt, J = 15.2, 5.3 Hz, 1H, H_2), 3.88–3.71 (br s, 2H, $2H_1$), 2.05 (s, 2H, $SiMe_2CH_2Ph$), 0.04 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (100.63 MHz, C_6D_6): δ 145.2 (d), 140.1 (s), 134.2 (d), 133.3 (d), 131.6 (d), 128.6 (d, 2×), 128.5 (d, 2×), 124.5 (d), 62.8 (t), 26.2 (t), −3.3 (q, 2×) ppm. **IR** (NaCl): ν 3500–3100 (br, O–H), 2953 (m, C–H), 1581 (m), 1492 (m), 1001 (s), 831 (s) cm^{-1}. **HRMS** (ESI$^+$): calcd for $C_{14}H_{21}OSi$ ($[M + H]^+$), 233.1356; found, 233.1357.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)-3-methylhexa-2,4-dien-1-ol 10f. To a solution of Pt(DVDS) (0.116 mL, 2% w/w in xylene, 0.005 mmol) and ^{t}Bu$_3$P (5.2 μL, 1 M in toluene, 0.005 mmol) in THF (5.1 mL), benzyldimethylsilane (0.102 g, 0.681 mmol) was added and the mixture was stirred for 30 min at 25 °C. A solution of (*E*)-methylhex-2-en-4-yn-1-ol **25** (0.05 g, 0.45 mmol) in THF (5.1 mL) was added and the resulting mixture was further stirred for 2.5 h. The solvent was removed and the residue was purified by flash-column chromatography (silica gel, 90 : 10 to 80 : 20 hexane/EtOAc) to afford 0.078 g (66%) of a colorless oil, which was identified as **10f**. **^{1}H NMR** (400.16 MHz C_6D_6): δ 7.15–7.12 (m, 2H, ArH), 7.05–6.91 (m, 3H, ArH), 6.14 (s, 1H, H_4), 5.53 (t, J = 6.6 Hz, H, H_2), 4.00 (d, J = 6.6 Hz, 2H, $2H_1$), 2.09 (s, 2H, $SiMe_2CH_2Ph$), 1.81 (s, 3H, C_5–CH_3), 1.57 (s, 3H, C_3–CH_3), 0.05 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 142.2 (d), 140.3 (s), 136.0 (s), 135.1 (s), 130.0 (d, 2×), 128.6 (d, 2×), 128.5 (d), 124.5 (d), 59.4 (t), 25.3 (t), 17.1 (q), 16.8 (q), −4.0 (q, 2×) ppm. **IR** (NaCl): ν 3600–3100 (br, O–H), 2954 (m, C–H), 1596 (m), 1250 (m), 998 (m) cm^{-1}. **UV** (MeOH): λ_{max} 226 nm. **MS** (ESI$^+$-TOF): m/z (%) 283 ($[M + Na]^+$, 100), 243 (10), 190 (5). **HRMS** (ESI$^+$): calcd for $C_9H_{14}OSi$ ($[M + Na]^+$), 283.1488; found, 283.1496.

All-*trans*-retinol 1a.

General procedure for the Hiyama–Denmark cross-coupling reaction. To a cooled (0 °C) solution of (2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-ol **10a** (0.12 g, 0.47 mmol) in THF (6.3 mL), TBAF (0.5 mL, 1 M in THF, 0.5 mmol) was added. After stirring for 30 min, a solution of (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (0.09 g, 0.31 mmol) in THF (3.2 mL) and Pd_2dba_3·$CHCl_3$ (0.03 g, 0.03 mmol) were added and the reaction mixture was stirred at 25 °C for 3.5 h. An aqueous solution of NH_4Cl was added and the resulting mixture was extracted with EtOAc (3×). The combined organic layers were washed with brine (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90 : 7 : 3 hexane/EtOAc/Et_3N) to afford 0.08 g (82%) of a red oil, which was identified as all-*trans*-retinol **1a**.[16]

General procedure for the Stille–Kosugi–Migita cross-coupling reaction. To a solution of Pd_2dba_3 (1 mg, 0.002 mmol) in degassed NMP (0.34 mL), $AsPh_3$ (0.5 mg, 0.002 mmol) was added. After stirring for 5 min, a solution of iodide **3** (20 mg, 0.063 mmol) in degassed NMP was added and the reaction mixture was stirred for 10 min. A solution of the stannane **9a** (31.8 mg, 0.082 mmol) in degassed NMP was then added and the resulting mixture was stirred at 25 °C overnight. An aqueous solution of KF was added and the mixture was extracted with EtOAc (3×). The combined organic layers were washed with water (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90 : 7 : 3 hexane/EtOAc/Et_3N), to afford 10.8 mg (60%) of a red oil, which was identified as all-*trans*-retinol **1a**.[16]

All-*trans*-13-demethyl-11-methylretinol 1b. Following the general procedure for the Hiyama–Denmark cross-coupling reaction, (2*E*,4*E*)-5-(benzyldimethylsilyl)-5-methylpenta-2,4-dien-1-ol **10b** (28.1 mg, 0.11 mmol), TBAF (0.25 mL, 1 M in THF, 0.25 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (30 mg, 0.1 mmol), and Pd_2dba_3·$CHCl_3$ (10.4 mg, 0.01 mmol) in THF (1.8 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hex/Et_3N; after injection: from 85 : 15 to 60 : 40 hexane/EtOAc), 7 mg (41%) of a yellow oil, which was identified as all-*trans*-13-demethyl-11-methylretinol **1b**.

Following the general procedure for the Stille–Kosugi–Migita cross-coupling reaction, (2*E*,4*E*)-5-(tributylstannyl)-hexa-

2,4-dien-1-ol **9b** (47.8 mg, 0.123 mmol), Pd_2dba_3 (2.2 mg, 0.002 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (0.030 g, 0.095 mmol), $AsPh_3$ (0.7 mg, 0.025 mmol) in NMP (1.5 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hexane/Et_3N; after injection: gradient from 85 : 15 to 60 : 40 hexane/EtOAc), 10 mg (37%) of a yellow oil, which was identified as all-*trans*-13-demethyl-11-methylretinol **1b**. **^{1}H NMR** (400.16 MHz, C_6D_6): 6.52 (ddt, J = 14.8, 11.2, 1.6 Hz, 1H, H_{13}), 6.36–6.24 (m, 2H, H_7 + H_8), 6.13 (d, J = 11.2 Hz, 1H, H_{12}), 6.05 (s, 1H, H_{10}), 5.66 (dt, J = 15.0, 5.7 Hz, 1H, H_{14}), 3.96–3.87 (m, 2H, $2H_{15}$), 2.01 (s, 3H, C_{11}–CH_3), 1.97 (t, J = 6.2 Hz, 2H, $2H_4$), 1.83 (s, 3H, C_9–CH_3), 1.80 (s, 3H, C_5–CH_3), 1.65–1.57 (m, 2H, $2H_3$), 1.52–1.47 (m, 2H, $2H_2$), 1.14 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 139.8 (d), 138.4 (s), 135.1 (d), 135.0 (s), 133.0 (d), 130.6 (d), 128.9 (s, 2×), 127.4 (d), 126.6 (d), 63.5 (t), 39.9 (t), 34.6 (s), 33.3 (t), 29.2 (q, 2×), 22.0 (q), 19.8 (t), 17.6 (q), 14.4 (q) ppm. **IR** (NaCl): ν 3500–3100 (br, O–H), 2955 (m, C–H), 1491 (m, C–H), 836 (s) cm^{-1}. **UV** (MeOH): λ_{max} (ε) 268 (14 100) nm. **MS** (ESI$^+$-TOF): m/z (%) 288 ($[M + H]^+$, 13), 287 ($[M]^+$, 12), 285 (13), 270 (18), 269 (100). **HRMS** (ESI$^+$): calcd for $C_{20}H_{31}O$ ($[M + H]^+$), 287.2405; found, 287.2369.

All-*trans*-13-demethyl-12-methylretinol 1c. Following the general procedure for the Hiyama–Denmark cross-coupling reaction, (2*E*,4*E*)-5-(benzyldimethylsilyl)-4-methylpenta-2,4-dien-1-ol **10c** (20.1 mg, 0.08 mmol), TBAF (0.18 mL, 1 M in THF, 0.18 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (0.02 g, 0.07 mmol), and Pd_2dba_3·$CHCl_3$ (0.007 g, 0.007 mmol) in THF (2.7 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hexane/Et_3N; after injection: gradient from 85 : 15 to 60 : 40 hexane/EtOAc) 19.5 mg (67%) of a yellow oil, which was identified as all-*trans*-13-demethyl-12-methylretinol **1c**.[55]

Following the general procedure for the Stille–Kosugi–Migita cross-coupling reaction, (2*E*,4*E*)-4-methyl-5-(tributylstannyl)-penta-2,4-dien-1-ol **9c** (24 mg, 0.062 mmol), Pd_2dba_3 (1 mg, 0.001 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (0.015 g, 0.05 mmol), and Ph_3As (3 mg, 0.01 mmol) in NMP (0.75 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hexane/Et_3N; after injection: gradient from 85 : 15 to 60 : 40 hexane/EtOAc), 6 mg (44%) of a yellow oil, which was identified as all-*trans*-13-demethyl-12-methylretinol **1c**.[55] **^{1}H NMR** (400.16 MHz, $(CD_3)_2CO$): δ 6.51–6.46 (m, 2H, H_7 + H_8), 6.43 (d, J = 17.1 Hz, 1H, H_{13}), 6.25–6.20 (m, 2H, H_{10} + H_{11}), 5.88 (dt, J = 15.7, 5.7 Hz, 1H, H_{14}), 4.19 (t, J = 5.4 Hz, 2H, $2H_{15}$), 2.09–2.02 (m, 2H, $2H_4$), 1.98 (s, 3H, C_{12}–CH_3), 1.92 (s, 3H, C_9–CH_3), 1.73 (s, 3H, C_5–CH_3), 1.67–1.60 (m, 2H, $2H_3$), 1.53–1.46 (m, 2H, $2H_2$), 1.05 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, $(CD_3)_2CO$): δ 139.4 (d), 138.8 (s), 136.7 (s), 135.7 (s), 135.6 (d), 129.9 (d), 129.7 (s), 127.9 (d), 127.5 (d), 127.1 (d), 63.5 (t), 40.4 (t), 35.0 (s), 33.7 (t), 29.4 (q, 2×), 22.1 (q), 20.0 (t), 12.9 (q), 12.7 (q) ppm. **UV** (MeOH): λ_{max} (ε) 331 (14 400) nm. **IR** (NaCl): ν 3500–3100 (br, O–H), 2925 (m, C–H), 2860 (m, C–H) cm^{-1}. **MS** (ESI$^+$-TOF): m/z (%) 270 (22), 269 ($[M - OH]^+$, 100), 139 (38). **HRMS** (ESI$^+$): calcd for $C_{20}H_{29}$ ($[M - OH]^+$), 269.4520; found, 269.2239.

All-*trans*-13-demethyl-14-methylretinol 1d. Following the general procedure for the Hiyama–Denmark cross-coupling reaction, (2*E*,4*E*)-5-(benzyldimethylsilyl)-4-methylpenta-2,4-dien-1-ol **10d** (37.2 mg, 0.15 mmol), TBAF (0.33 mL, 1 M in THF, 0.33 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (40 mg, 0.13 mmol), and Pd_2dba_3·$CHCl_3$ (13.5 mg, 0.013 mmol) in THF (2.6 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hexane/Et_3N; after injection: from 85 : 15 to 60 : 40 hexane/EtOAc), 23 mg (62%) of a yellow oil, which was identified as all-*trans*-13-demethyl-14-methylretinol **1d**.[16,17]

Following the general procedure for the Stille–Kosugi–Migita reaction, (2*E*,4*E*)-2-methyl-5-(tributylstannyl)-penta-2,4-dien-1-ol **9d** (31.8 mg, 0.082 mmol), Pd_2dba_3 (1.4 mg, 0.002 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (0.020 g, 0.064 mmol), and Ph_3As (0.4 mg, 0.002 mmol) in NMP (1 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hexane/Et_3N; after injection: gradient from 85 : 15 to 60 : 40 hexane/EtOAc), 4 mg (22%) of a yellow oil, which was identified as all-*trans*-13-demethyl-14-methylretinol **1d**.[16,17] **^{1}H NMR** (400.16 MHz, C_6D_6): δ 6.66 (dd, J = 14.6, 11.3 Hz, 1H, H_{11}), 6.51 (dd, J = 14.6, 11.1 Hz, 1H, H_{12}), 6.40–6.28 (m, 2H, H_7 + H_8), 6.26 (d, J = 10.9 Hz, 1H, H_{10}), 6.19 (dq, J = 11.1, 1.5 Hz, 1H, H_{13}), 3.79 (br s, 2H, $2H_{15}$), 1.97 (t, J = 6.3 Hz, 2H, $2H_4$), 1.88 (s, 3H, C_{14}–CH_3), 1.81 (d, J = 0.9 Hz, 2H, C_9–CH_3), 1.66–1.54 (m, 5H, $2H_3$ + C_5–CH_3), 1.52–1.44 (m, 2H, $2H_2$), 1.14 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 138.6 (d), 138.4 (s), 137.9 (s), 135.7 (s), 131.4 (d), 129.5 (d), 129.3 (d), 128.1 (s), 126.8 (d), 125.6 (d), 68.3 (t), 40.0 (t), 34.6 (s), 33.4 (t), 29.2 (q, 2×), 22.0 (q), 19.8 (t), 14.2 (q), 12.8 (q) ppm. **IR** (NaCl): ν 3357 (br, O–H), 2925 (m, C–H), 2857 (m, C–H), 1641 (m, C–H), 968 (s) cm^{-1}. **UV** (MeOH): λ_{max} (ε) 331 (12 000) nm. **MS** (ESI$^+$-TOF): m/z (%) 287 ($[M + H]^+$, 19), 285 (12), 279 (12), 270 (20), 269 (100). **HRMS** (ESI$^+$): calcd for $C_{20}H_{31}O$ ($[M + H]^+$), 287.2372; found, 287.2369

All-*trans*-13-demethylretinol 1e. Following the general procedure for the Hiyama–Denmark cross-coupling reaction, (2*E*,4*E*)-5-(benzyldimethylsilyl)penta-2,4-dien-1-ol **10e** (20.9 mg, 0.09 mmol), TBAF (0.2 mL, 1 M in THF, 0.2 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (23.7 mg, 0.075 mmol), and Pd_2dba_3·$CHCl_3$ (7.8 mg, 0.007 mmol) in THF (3 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hexane/Et_3N; after injection: gradient from 85 : 15 to 60 : 40 hexane/EtOAc), 17.5 mg (86%) of a yellow oil, which was identified as all-*trans*-13-demethylretinol **1e**.[56]

Following the general procedure for the Stille–Kosugi–Migita cross-coupling reaction, (2*E*,4*E*)-5-(tributylstannyl)-penta-2,4-dien-1-ol **9e** (23 mg, 0.062 mmol), Pd_2dba_3 (1 mg, 0.001 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (0.015 g, 0.05 mmol), and Ph_3As (3 mg, 0.01 mmol) in NMP (0.75 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first

with 98 : 2 hexane/Et_3N; after injection: gradient from 85 : 15 to 60 : 40 hexane/EtOAc), 4 mg (31%) of a yellow oil, which was identified as all-*trans*-13-demethylretinol **1e**.[57] **^{1}H NMR** (400.16 MHz, C_6D_6): δ 6.58 (t, J = 12.2 Hz, 1H, H_{11}), 6.36–6.27 (m, 2H, H_7 + H_8), 6.27–6.15 (m, 3H, H_{10} + H_{12} + H_{13}), 5.67–5.56 (m, 1H, H_{14}), 3.92–3.85 (br s, 2H, $2H_{15}$), 1.96 (t, J = 6.5 Hz, 2H, $2H_4$), 1.84 (s, 3H, C_9–CH_3), 1.79 (s, 3H, C_5–CH_3), 1.65–1.56 (m, 2H, $2H_3$), 1.52–1.45 (m, 2H, $2H_2$), 1.13 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 138.5 (d), 138.3 (s), 136.2 (s), 132.9 (d), 132.7 (d), 131.5 (d), 130.8 (d), 129.7 (d), 129.3 (s), 127.1 (d), 63.3 (t), 39.9 (t), 34.6 (s), 33.3 (t), 29.2 (q, 2×), 22.0 (t), 19.7 (q), 12.7 (q) ppm. **IR** (NaCl): ν 3500–3100 (br, O–H), 2928 (m, C–H), 2862 (m, C–H), 984 (s) cm^{-1}. **UV** (MeOH): λ_{max} (ε) 269 (11 600) nm. **MS** (ESI$^+$-TOF): m/z (%) 273 ([M + H]$^+$, 1), 272 (2), 271 (1), 256 (20), 255 (100). **HRMS** (ESI$^+$): calcd for $C_{19}H_{28}O$ ([M + H]$^+$) 273.2158; found, 273.2212.

All-*trans*-11-methylretinol 1f. Following the general procedure for the Hiyama–Denmark cross-coupling reaction, (2*E*–4*E*)-5-(benzyldimethylsilyl)-3-methylhexa-2,4-dien-1-ol **10f** (18 mg, 0.06 mmol), TBAF (0.15 mL, 1 M in THF, 0.15 mmol), (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **3** (17.7 mg, 0.07 mmol), and Pd_2dba_3·$CHCl_3$ (6.2 mg, 0.006 mmol) in THF (1 mL) afforded, after purification by flash-column chromatography (silica gel, equilibrated first with 98 : 2 hexane/Et_3N; after injection: from 85 : 15 to 60 : 40 hexane/EtOAc), 7 mg (41%) of a yellow oil, which was identified as all-*trans*-11-methylretinol **1f**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 6.33–6.26 (m, 2H, H_7 + H_8), 6.05 (s, 1H, H_{10}), 5.90 (s, 1H, H_{12}), 5.57 (t, J = 6.7 Hz, 1H, H_{14}), 4.01 (d, J = 6.5 Hz, 2H, $2H_{15}$), 2.03 (s, 3H, C_{13}–CH_3), 2.01–1.95 (m, 2H, $2H_4$), 1.91 (s, 3H, C_{11}–CH_3), 1.86–1.81 (m, 2H, $2H_3$), 1.81 (s, 3H, C_9–CH_3), 1.61 (s, 3H, C_5–CH_3), 1.55–1.48 (m, 2H, $2H_2$), 1.15 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 139.6 (d), 138.4 (s), 135.8 (d), 135.0 (s), 134.6 (s), 134.2 (d), 134.2 (s), 130.1 (d), 128.9 (s), 126.6 (d), 59.6 (t), 39.9 (t), 34.6 (s), 33.2 (t), 29.2 (q, 2×), 22.0 (q), 19.8 (t), 19.4 (q), 17.4 (q), 14.3 (q) ppm. **IR** (NaCl): ν 3500–3100 (br, O–H), 2923 (m, C–H), 1643 (m, C–H), 969 (s) cm^{-1}. **UV** (MeOH): λ_{max} (ε) 266 (11 800) nm. **MS** (ESI$^+$-TOF): m/z 301 ([M + H]$^+$, 100), 284 (22), 283 (100). **HRMS** (ESI$^+$): calcd for $C_{21}H_{33}O$ ([M + H]$^+$), 301.2525; found, 301.2525.

All-*trans*-retinal 2a. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of all-*trans*-retinol **1a** (12 mg, 0.042 mmol), MnO_2 (36.4 mg, 0.419 mmol) and Na_2CO_3 (44.4 mg, 0.419 mmol) in Et_2O (39 mL), afforded 9 mg (76%) of a yellow oil, which was identified as all-*trans*-retinal **2a**.[57] **UV** (MeOH): λ_{max} (ε) 377 (10 000) nm.

All-*trans*-13-demethyl-11-methylretinal 2b. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of all-*trans*-13-demethyl-11-methylretinol **1b** (8.6 mg, 0.03 mmol), MnO_2 (26.1 mg, 0.30 mmol) and Na_2CO_3 (31.8 mg, 0.30 mmol) in Et_2O (1.2 mL) afforded 7.4 mg (88%) of a yellow oil, which was identified as all-*trans*-13-demethyl-11-methylretinal **2b**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 9.58 (d, J = 7.6 Hz, 1H, H_{15}), 6.65 (d, J = 15.9 Hz, 1H, H_7), 6.51 (d, J = 12.1 Hz, 1H, H_{12}), 6.40 (d, J = 15.9 Hz, 1H, H_8), 6.29 (s, 1H, H_{10}), 6.25 (d, J = 15.4, 12.1 Hz, 1H, H_{13}), 6.11 (dd, J = 15.4, 7.6 Hz, 1H, H_{14}), 1.95 (t, J = 6.1 Hz, 2H, $2H_4$), 1.82 (s, 3H, C_{11}–CH_3), 1.74 (s, 3H, C_9–CH_3), 1.64–1.55 (m, 2H, $2H_3$), 1.50–1.44 (m, 2H, $2H_2$), 1.51 (s, 3H, C_5–CH_3), 1.12 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 192.3 (d), 155.6 (s), 141.5 (s), 138.3 (d), 138.1 (s), 135.8 (d), 134.0 (s), 130.4 (s), 129.7 (d), 127.7 (d), 126.3 (d), 39.9 (t), 34.6 (s), 33.4 (t), 29.2 (q, 2×), 22.0 (q), 19.6 (t), 12.8 (q), 12.3 (q) ppm. **IR** (NaCl): ν 2924 (m, C–H), 1674 (s, C═O), 1596 (s), 1124 (s), 965 (m) cm^{-1}. **UV** (MeOH): λ_{max} (ε) 381 (15 600) nm. **HRMS** (ESI$^+$): calcd for $C_{20}H_{29}O$ ([M + H]$^+$), 285.2212; found, 285.2212.

All-*trans*-13-demethyl-12-methylretinal 2c. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of all-*trans*-13-demethyl-12-methylretinol **1c** (20 mg, 0.07 mmol), MnO_2 (60.7 mg, 0.698 mmol) and Na_2CO_3 (74 mg, 0.698 mmol) in Et_2O (2.8 mL) afforded 15.4 mg (76%) of a yellow oil, which was identified as all-*trans*-13-demethyl-12-methylretinal **2c**.[16,17] **UV** (MeOH): λ_{max} (ε) 381 (17 900) nm.

All-*trans*-13-demethyl-14-methylretinal 2d. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of all-*trans*-13-demethyl-14-methylretinol **1d** (20 mg, 0.070 mmol), MnO_2 (60.7 mg, 0698 mmol) and Na_2CO_3 (74 mg, 0.698 mmol) in Et_2O (2.7 mL) afforded 16.3 mg (82%) of a yellow oil, which was identified as all-*trans*-13-demethyl-14-methylretinal **2d**.[16,17] **UV** (MeOH): λ_{max} (ε) 377 (13 000) nm.

All-*trans*-13-demethylretinal 2e. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of all-*trans*-13-demethylretinol **1e** (30.2 mg, 0.111 mmol), MnO_2 (96.4 mg, 0.111 mmol) and Na_2CO_3 (117.5 mg, 0.111 mmol) in Et_2O (4.4 mL) afforded 18.1 mg (60%) of a yellow oil, which was identified as all-*trans*-13-demethylretinal **2e**. **^{1}H NMR** (400.16 MHz, C_6D_6): δ 9.50 (d, J = 7.8 Hz, 1H, H_{15}), 6.66–6.48 (m, 2H), 6.39 (d, J = 16.1 Hz, 1H, H_8), 6.23 (d, J = 16.1 Hz, 1H, H_7), 6.07–5.90 (m, 3H), 1.95 (t, J = 5.9 Hz, 2H, $2H_4$), 1.76 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.63–1.52 (m, 2H, $2H_3$), 1.51–1.42 (m, 2H, $2H_4$), 1.11 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 192.2 (d), 151.0 (d), 141.3 (s), 138.1 (d), 138.0 (s) 137.8 (d), 131.1 (d), 130.6 (s), 130.3 (d), 130.0 (d), 129.9 (d), 39.9 (t), 34.6 (q), 33.4 (t), 29.2 (q, 2×), 21.9 (q), 19.6 (t), 12.8 (q) ppm. **UV** (MeOH): λ_{max} (ε) 377 (19 700) nm. **IR** (NaCl): ν 2925 (m, C–H), 1674 (m, C═O), 1577 (s), 1155 (s), 983 (s) cm^{-1}. **HRMS** (ESI$^+$): calcd for $C_{19}H_{27}O$ ([M + H]$^+$) 271.2056; found, 271.2056.

All-*trans*-11-methylretinal 2f. Following the general procedure for MnO_2 oxidation of allylic alcohols, the reaction of all-*trans*-11-methylretinol **1f** (26.5 mg, 0.088 mmol), MnO_2 (76.7 mg, 0.882 mmol) and Na_2CO_3 (93.5 mg, 0.882 mmol) in Et_2O (3.5 mL) afforded 17 mg (65%) of a yellow oil, which was identified as **2f**. The ^{1}H NMR spectrum showed this compound to be a *ca.* 10 : 1 mixture of isomers. Data for the major all-*trans* isomer: **^{1}H NMR** (400.16 MHz, C_6D_6): δ 9.97 (d, J = 7.8 Hz, 1H, H_{15}), 6.24 (app t, J = 17.6 Hz, 2H, H_7 + H_8), 6.01 (d, J = 7.8 Hz, 1H, H_{14}), 5.86 (s, 1H, H_{12} or H_{14}), 5.68 (s, 1H, H_{12} or H_{14}), 1.96 (t, J = 6.1 Hz, 2H, $2H_4$), 1.87 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.63–1.56 (m, 2H, $2H_3$), 1.52–1.43 (m, 2H, $2H_2$), 1.13 (s, 6H, C_1–$(CH_3)_2$) ppm. **^{13}C NMR** (101.63 MHz, C_6D_6): δ 189.9 (d), 154.1 (s), 141.0 (s), 139.0 (d), 138.2 (s), 136.9 (s), 135.0 (d), 132.7 (d), 129.6 (s), 127.9 (d), 127.8 (d), 39.9 (t), 34.6 (s), 33.2 (t), 29.2 (q, 2×), 21.9 (q), 20.1 (q), 19.7 (t), 17.8 (q), 14.3 (q) ppm. **IR** (NaCl): ν 2925 (s, C–H),

2862 (m, C–H), 1662 (s, C═O), 1573 (m), 1130 (m), 896 (w) cm^{-1}. **UV** (MeOH): λ_{max} (ε) 364 (13 400) nm. **HRMS** (ESI^+): calcd for $C_{21}H_{31}O$ ($[M + H]^+$), 299.2371; found, 299.2369.

Conflicts of interest

The authors declare no conflicts of interest.

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