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Cross-Coupling Reactions of Organosilicon Compounds in the Stereocontrolled Synthesis of Retinoids

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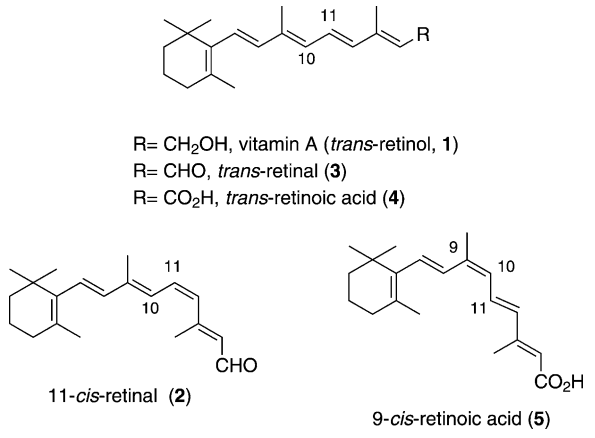
Abstract: This paper presents a full account of the use of Hiyama cross-coupling reactions in a highly convergent approach to retinoids in which the key step is construction of the central C10–C11 bond. Representatives of two families of oxygen-activated dienyl silanes (ethoxysilanes and silanols) and of all reported families of "safety-catch" silanols (siletanes, silyl hydrides, allyl-, benzyl-, aryl-, 2-pyridyl- and 2-thienyl-silanes) were regio- and stereoselectively prepared and stereospecifically coupled to an appropriate electrophile by treatment with a palladium catalyst and a nucleophilic activator. Both all-*trans* and 11-*cis*-retinoids, and their chain-demethylated analogues, were obtained in good yields regardless of the geometry (*E*/*Z*) and of the steric congestion in each fragment. This comprehensive study conclusively establishes the Hiyama cross-coupling reaction, with its mild reaction conditions and stable, easily prepared, ecologically advantageous silicon-based coupling partners, as the most effective route to retinoids reported to date.

Keywords: C–C coupling · organic synthesis · retinoids · silicon · stereochemistry

Introduction

The term retinoid collectively describes a class of over 4000 natural or synthetic molecules that are structurally and/or functionally related to vitamin A (*trans*-retinol, **1**). Native retinoids play crucial roles in a variety of biological processes that are critically dependent on the geometry of the polyene side chain and the nature of its polar terminal group.[1] All-*trans*-retinol (**1**) is required for the normal development of many cell types, and is the precursor for many other retinoids.[2] Retinaldehydes act as chromophores in protein photoreceptors:[3] 11-*cis*-retinal (**2**) is the ligand of rhodopsin, the pigment responsible for light absorption in the visual process,[4] and all-*trans*-retinal (**3**) binds to bacteriorhodopsin, the light-driven proton pump in *Halobacterium salinarium*.[5] All-*trans*- and 9-*cis*-retinoic acids (**4** and **5**, respectively) are nuclear signalling molecules, **4** targeting retinoic acid receptors (RARs) and **5** retinoic X receptors (RXRs); both play essential roles in vertebrate growth and development, the immune response and reproduction.[6]



In recent decades, a wide range of synthetic retinoids have been prepared. Some have been used to study the complex biological processes mentioned above, some have been investigated as possible therapeutic agents with greater potency and/or less toxicity than natural retinoids, and some have been designed for specific technological applications.[7] However, fuller exploration of the potential of retinoids in these important fields of application has been held back by the difficulties of their efficient synthesis, which centre on two main issues: first, the sensitivity of the polyene system to light, oxygen and many common synthetic reagents and second, the control of stereochemistry during the formation of each double bond.[8]

In this latter respect, strategies based on classical olefin elongation procedures (Wittig, Horner–Emmons, Peterson and Julia reactions) have been successfully applied to the *trans*-series but have often afforded *cis*-retinoids as mixtures of isomers.[9] As a consequence, more stereoselective ap-

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proaches have had to be developed. In particular, transition-metal-catalysed cross-coupling reactions between organometallic nucleophiles and organic electrophiles[10] (notably the Negishi, Suzuki–Miyaura and Stille–Kosugi–Migita reactions) have been extensively applied to the stereospecific synthesis of both all-*trans* and *cis* retinoids, and currently provide the main access route to these highly conjugated polyenes.[11]

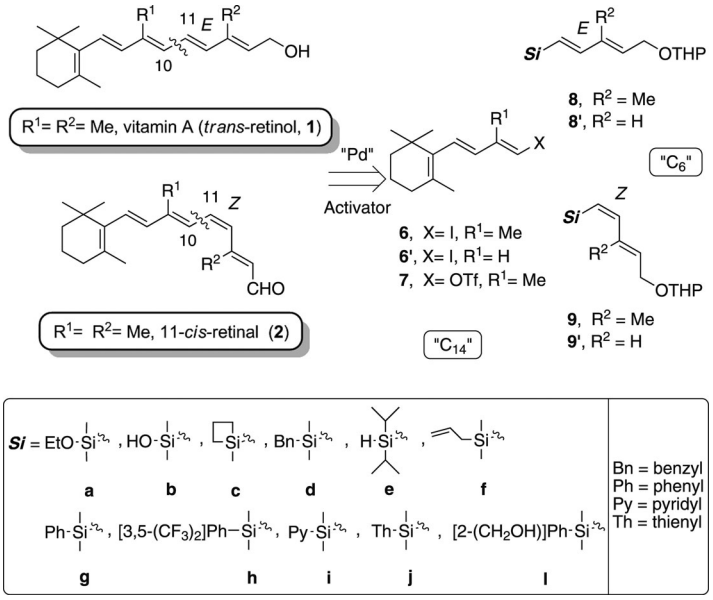
Unfortunately, even these powerful cross-coupling methods suffer from a number of major drawbacks, most of them related to the nature of the organometallic donors. For instance, even though organostannanes can be reacted with a diverse assortment of electrophiles, large excesses and forcing conditions are sometimes required to prevent homodimerization of the organotin reagent, and removal of the toxic tin byproducts is irksome. Some boronic acids and esters are difficult to synthesise and purify, undergo degradation during extended storage (some need to be prepared in situ) and can suffer protiodeborylation under cross-coupling conditions. In addition, *E*/*Z* selectivity can be partially lost in both reactions in certain cases of low reactivity.[12] Finally, although highly stereoselective syntheses of vitamin A by using Negishi reactions have been reported,[11a,b] drawbacks such as the sensitivity of organozincs to moisture and oxygen seem likely to be responsible for the scarce use of these reagents in this field. The development of organometallics that are more cost effective, easier to prepare and handle and less toxic than existing compounds is therefore still an active area of research.[13]

In the past decade, considerable attention has focused on the synthetic use of silicon-containing reagents, which are stable, easily introduced into organic substrates, applicable to a wide range of chemical transformations and relatively non-toxic. Though inherently reluctant to cross-couple (because C–Si bonds have no significant associated dipole), this impediment was successfully overcome by Hiyama and coworkers.[14] Since then, numerous heteroatom-functionalised silicon moieties, including halosilanes, oxysilanes, silanols, cyclic silyl ethers and polysiloxanes, have been shown to undergo cross-coupling under mild conditions with aryl, alkenyl, alkynyl and alkyl electrophiles upon treatment with an appropriate palladium catalyst and a nucleophilic promoter. Furthermore, the scope of the reaction has been extended by the advent of "safety-catch" silanols,[15] which are stable under conditions that heteroatom-substituted silanes may not tolerate, but which can nonetheless be activated for cross-coupling in situ. Hiyama cross-coupling is now a well-established methodology for the synthesis of organic materials[16] and complex natural products.[14l]

As part of our ongoing research into the chemistry and biology of natural and synthetic retinoids,[17] we recently reported the first application of the Hiyama reaction to the synthesis of these highly conjugated metabolites. We found that in this field too, organosilicon-based cross-coupling reactions can compete advantageously with the Suzuki and Stille methodologies.[18] We present herein the full details of that research. To gain insight into the behaviour of the reaction in constructing such an unstable system as the retinoid backbone, the longest polyolefin ever prepared by this means,[19] we synthesized the natural *trans* and *cis* retinoids **1** and **2** and, in both cases, protected analogues lacking one or both the 9- and 13-methyl groups. To determine the influence of the substituent on the silicon atom, the protected analogues were synthesized by using as many as possible of a large set of organosilicon reagents that included representatives of two families of oxygen-activated silanes and of the whole array of "masked silanols" reported to date.[20] These organosilicon reagents were prepared by existing methods and evaluated and compared with regard to their chemical stability, activation conditions (fluoride-promoted or fluoride-free) and suitability for these specific cross-coupling reactions.[21]

Results and Discussion

As in our previous Suzuki and Stille approaches to retinoids, we employed the highly convergent "$C_{14}+C_6$" strategy,[22] in which the key step is the construction of the central single bond C10–C11 (Scheme 1).[11e,17c] The C_{14} electrophiles (trienyl iodides **6** and **6′** and triflate **7**) were readily obtained



Scheme 1. Retrosynthetic analysis.

from β-ionone by following standard synthetic routes.[11e,17c] As the C_6 organometallic partners we used *trans*-dienylsilanes **8** and **8′** and *cis*-dienylsilanes **9** and **9′**, in each case with as many as possible of a wide range of silane moieties comprising representatives of two families of oxygen-activated silanes (ethoxysilane **a** and silanol **b**) and of the whole collection of "safety-catch" silanols (siletane **c**, benzylsilane **d**, silyl hydride **e**, allylsilane **f**, phenylsilane **g**, bistrifluoromethylphenylsilane **h**, pyridylsilane **i**, thiophenylsilane **j** and

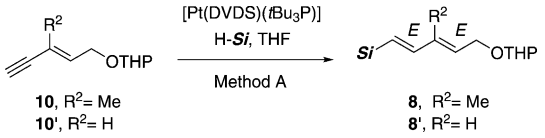
"reusable"[23] [2-(hydroxylmethyl)phenyl]silane **l**). For regio- and stereoselective preparation of these metallic intermediates, four well-established protocols were examined: transition-metal-catalysed hydrosilylation of alkynes (method A), palladium-catalysed silylation or metal–halogen exchange/carbanion silylation of vinyl halides (methods B and C, respectively) and stereoselective reduction of alkynylsilanes (method D).

Synthesis of (1*E*,3*E*)-dienylsilanes 8 and 8′ and (1*Z*,3*E*)-dienylsilanes 9 and 9′

*Method A: Transition-metal-catalysed hydrosilylation of enynes **10** and **10′***: Hydrosilylation of alkynes is the simplest and most straightforward approach to alkenylsilanes. The regio- and stereochemical outcome of the reaction depends on factors such as the catalytic system employed (the metal and its ligands), the substituents on the hydrosilane, reaction parameters, such as solvent and temperature, and sometimes even the order in which the reagents are added.[24] Pt-based complexes usually ensure exclusive *syn*-addition, affording β-(*E*)-alkenylsilanes (the thermodynamic products), whereas β-(*Z*) products can be obtained stereoselectively by using Rh, Ir and Ru catalysts. In fact, by changing their ligands, Rh and Ru can be "tuned" to afford either diastereomer.[25,26] Faller and D'Alliessi[25] found that although the neutral rhodium dimer $[(Cp^*RhCl_2)_2]$ (Cp^* = pentamethylcyclopentadienyl) promoted the atypical *anti* addition of trialkyl- and trialkoxy-substituted silanes to acetylene, yielding the *Z* isomers, the dicationic complex $[\{Rh(BINAP)Cp^*\}(SbF_6)_2]$ (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) formed the (*E*)-vinylsilanes. Ozawa and co-workers[26] reported that the reaction of an alkyne with a hydrosilane containing aromatic substituents led to the corresponding (*E*)-vinylsilane if performed in the presence of the ruthenium hydride catalyst $[RuCl(CO)(H)(PPh_3)_2]$, and to the (*Z*)-vinylsilane if the rutheniumsilyl complex $[RuCl(CO)(PiPr_3)_2(SiMe_2Ph)]$ was used. Still more remarkably, Mori and co-workers[27] have found that whether $[RhI(PPh_3)_3]$ affords (*E*)- or (*Z*)-alkenylsilanes (in both cases with excellent stereoselectivity) depends simply on the order of addition of the reagents and the reaction conditions: when the alkyne is added to a mixture of hydrosilane and the catalyst, (*Z*)-alkenylsilanes are obtained, whereas adding the catalyst to a mixture of the silane and alkyne and then heating at 60 °C affords *E* products.

In this work, we first investigated selective *syn* hydrosilylation of O-protected enynols **10** and **10′** to obtain (1*E*,3*E*)-dienylsilanes **8** and **8′**. In preliminary screening runs with siloxane **8a** as the target, [Pt(DVDS)(*t*Bu$_3$P)] (DVDS = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane),[28] which is soluble in organic solvents, was significantly more efficient (yield 92% after 1 h in THF) than $[PtCl_2(cod)]$ (cod = 1,5-cyclooctadiene; CH_2Cl_2, 65%), $[RhI(PPh_3)_3]$ (toluene, 60 °C, 62%) or $[RuCl(CO)(H)(PPh_3)_2]$ (CH_2Cl_2, 48%). All of the (*E*)-vinylsilanes **8** and **8′** except **8c** and **8′c** (for which the required hydrosilane is not commercially available) were then regio- and stereoselectively synthesized by using [Pt(DVDS)(*t*Bu$_3$P)], in most cases in excellent yield (Table 1) in spite of the steric hindrance of the enyne precursor, although minor departures from the standard conditions (THF, RT, 1 h) had to be introduced in some cases (see the Supporting Information). The most noteworthy of these departures concerned the preparation of pyridylsilanes **8i** and **8′i**, which required 5 h in toluene at 100 °C. Also, silanols **8b** and **8′b** were obtained indirectly from siloxanes **8a** and **8′a** (CH_3CN, 1.0 M HOAc/NaOAc buffer, pH 5)[29] in 89 and 85% overall yield, respectively, for the one-pot silylation–hydrolysis procedure. Similarly, [2-(hydroxymethyl)phenyl]silanes **8l** and **8′l** were prepared from **8k** and **8′k** by deprotection under basic conditions (K_2CO_3, H_2O/CH_3OH)[23] in 57 and 48% combined yield for the two steps.

Table 1. Synthesis of (1*E*,3*E*)-dienylsilanes **8** and **8′** by Pt-catalysed hydrosilylation of *E* enynes **10** and **10′** (method A).



10, R^2 = Me; **10′**, R^2 = H — **8**, R^2 = Me; **8′**, R^2 = H

Entry	Silane	H-*Si*	**8**	**8′**
1	**a**	$HMe_2(OEt)Si$	92	85
2	**b**[a]	$HMe_2(OEt)Si$	89	85
3	**c**[b]	–	–	–
4	**d**	HMe_2BnSi	97	97
5	**e**	H_2iPr_2Si	95	73
6	**f**	$HMe_2allylSi$	85	88
7	**g**	HMe_2PhSi	99	95
8	**h**	$HMe_2[3,5\text{-}(CF_3)_2]PhSi$	92	83
9	**i**[c]	$HMe_2$2-PySi	98	91
10	**j**	$HMe_2$2-ThSi	91	92
11	**k**	$HMe_2[2\text{-}(CH_2OAc)Ph]Si$	63	55
12	**l**[d]	$HMe_2[2\text{-}(CH_2OAc)Ph]Si$	57	48

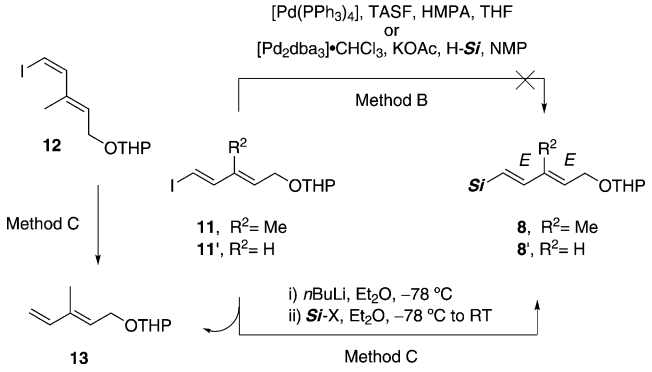
[a] Followed by acid hydrolysis: CH_3CN, 1.0 M HOAc/NaOAC buffer, pH 5, 8 h. [b] This hydrosilane is not available. [c] Reaction carried out in toluene at 100 °C. [d] Followed by removal of acetoxymethylphenyl: K_2CO_3, H_2O/CH_3OH.

Unexpectedly, the *anti* hydrosilylation of **10** and **10′** proved to be much more complicated. In our hands, none of the stereodivergent conditions described by the groups of Faller ($[RhCl_2(Cp^*)]_2$, CH_2Cl_2),[25] Ozawa ($[RuCl(CO)(PiPr_3)_2(SiMe_2Ph)]$, CH_2Cl_2)[26] or Mori ($[RhI(PPh_3)_3]$, toluene, 0 °C)[27] led to the desired (1*Z*,3*E*)-dienylsilanes **9** and **9′**. In all cases, mixtures of stereoisomers were obtained, which we attributed to isomerization of the initially produced *Z* vinylsilanes through an insertion–β-elimination mechanism in the presence of a catalytic amount of hydrosilane and the Rh or Ru catalysts.[30]

*Method B: Palladium-catalysed silylation of dienyl iodides **11** and **12**:* Although catalytic cross-coupling of organic halides to silicon compounds, such as disilanes, monohydrosilanes or dihydrosilanes, with Pd, Rh or Pt complexes as catalysts, is a useful route to functionalized arylsilanes,[31] only a few examples of its use for the synthesis of alkenylsilanes have been reported. Notable among them are Hiyama's syn-

thesis of vinyl- and dienylsilanes by coupling the precursor halides with hexamethyldisilane under tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TASF)-promoted Pd^0 catalysis ($[Pd(PPh_3)_4]$, TASF, hexamethylphosphoramide (HMPA), THF),[32] and Masuda's selective silylation of alkenyl iodides with hydrosilanes by using $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone) as the catalyst, KOAc as the base and amide solvents (*N*-methylpyrrolidone (NMP)).[33] Discouragingly, in this work, neither of these specific protocols allowed the preparation of (1*E*,3*E*)-dienylsilanes **8** from iodide **11** or of (1*Z*,3*E*)-dienylsilanes **9** from iodide **12**; only starting materials or complex reaction mixtures were obtained (Table 2). The same dissuasive results were provided by several conditions previously reported for silylation of aryl halides by using platinum ($Me_2EtOSiH$, PtO_2, AcONa, NMP)[31j] or rhodium ($Me_2EtOSiH$, $[\{RhCl(cod)\}_2]$, Et_3N, DMF).[31i]

Table 2. Attempts to synthesize (1*E*,3*E*)-dienylsilanes **8** and **8′** from dienyliodides **11** and **11′** by metal-catalysed cross-coupling to a silicon nucleophile (method B) and by lithium–halogen exchange followed by anion trapping with a silicon electrophile (method C).



Entry	Silane	*Si*-X	**8**	**8′**
1	**b**	D_3[a]	80	74
2	**c**	$Me(CH_2)_3SiCl$	86	96

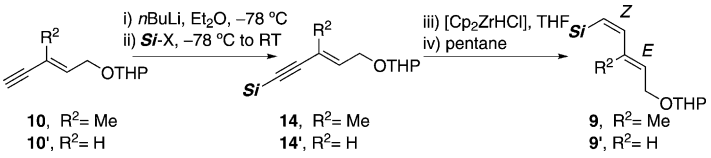
[a] D_3 = Hexamethylcyclotrisiloxane.

*Method C: Halogen–lithium exchange in dienyl iodides **11**, **11′** and **12**, followed by trapping with a silicon electrophile*: The use of organolithium and organomagnesium reagents for the nucleophilic displacement of a leaving group at a silicon centre is a classical means of introducing silicon into an organic molecule.[34] Direct formation of organosilanols can similarly be accomplished by addition of the organometallic reagent to a number of inexpensive cyclosiloxanes followed by in situ aqueous hydrolysis of the polysiloxane intermediate.[35]

In this work, metalation of (1*E*,3*E*)-dienyl iodides **11** and **11′** with *n*BuLi in ether, followed by trapping of the resulting anions with hexamethylcyclotrisiloxane (D_3) or chloromethylsilacyclobutane, afforded silanols **8b** and **8′b**, and siletanes **8c** and **8′c**, in high yields (Table 2). Surprisingly, however, failure met all attempts to obtain derivatives **8d–l** and **8′d–l** by trapping the same vinyl anions with other commercially available chlorosilanes (benzyldimethylchlorosilane, diisopropylchlorosilane, allyldimethylchlorosilane, aryl- and heteroaryldimethylchlorosilanes) or with 1,1-dimethyl-2-oxa-1-silaindan.[23] Moreover, it was impossible to obtain any of the (1*Z*,3*E*)-dienylsilanes **9** by applying this method to precursor iodide **12**. In all of these unfruitful attempts, the main reaction product after workup was the terminal alkene **13** (Table 2), the anions generated having been unable to trap the silicon electrophiles.

*Method D: cis-Selective reduction of 1-alkynylsilanes **14** and **14′***: In view of the apparent impossibility of preparing (1*Z*,3*E*)-dienylsilanes **9** and **9′** by means of one-step protocols, we turned to a two-step sequence based on the *cis*-selective reduction of 1-alkynylsilane precursors (Table 3).

Table 3. Synthesis of (1*Z*,3*E*)-dienylsilanes **9** and **9′** by *cis*-selective reduction of 1-alkynylsilane precursors **14** and **14′** (method D).



Entry	Silane	*Si*-X	**14**	**14′**	**9**	**9′**
1	**c**	$Me(CH_2)_3SiCl$	90	93	77	68
2	**d**	$Me_2BnSiCl$	92	87	76	76
3	**e**	$HiPr_2SiCl$	90	99	58	49
4	**f**[a]	$Me_2allylSiCl$	91	89	–	–
5	**g**	$Me_2PhSiCl$	71	83	50	52
6	**h**	$Me_2[3,5\text{-}(CF_3)_2]PhSiCl$	88	99	60	52
7	**b**[b]		–	–	53	69

[a] Reaction with $[ZrCl(Cp)_2(H)]$ leads to over-reduction of the allyl group. [b] Diisopropylsilanols obtained by oxidation of diisopropylhydrosilanes **9e** and **9′e** ($[RuCl_2(para\text{-cymene})_2]$, acetonitrile, H_2O; overall yield).

Compounds **14c–h** and **14′c–h** were obtained uneventfully by metalation of enynes **10** and **10′** (*n*BuLi, Et_2O, −78 °C) and anion trapping with the corresponding chlorosilanes.[36]

Our initial attempts at *cis* reduction of the alkynylsilanes failed: hydrogenation by using the Lindlar catalyst,[37] reaction with diisobutylaluminium hydride (DIBAL) under various protocols[38] and reaction with a diimide precursor under mildly basic conditions,[39] all gave poor yields and/or resulted in over-reduction. Eventually, however, reaction with $[ZrCl(Cp)_2(H)]$[40] (Cp = cyclopentadienyl) in pentane afforded moderate to good yields of all of **9c–h** and **9′c–h** except **9f** and **9′f** (Table 3).[41] Similar yields were obtained in all cases by generating the Schwartz reagent in situ $[ZrCl_2(Cp)_2 + DIBAL]$.[42] Silanols **9b** and **9′b** were subsequently prepared from hydrosilanes **9e** and **9′e** by ruthenium-catalysed hydrolytic oxidation ($[RuCl_2(para\text{-cymene})]_2$, H_2O, 1:1 benzene/CH_3CN, 1 h).[43]

Synthesis of (1*E*,3*E*)-1,3-dienylsilanes 8 and 8′ and (1*Z*,3*E*)-1,3-dienylsilanes 9 and 9′: Summary and characterization: All of the targeted (1*E*,3*E*)-dienylsilanes were obtained in

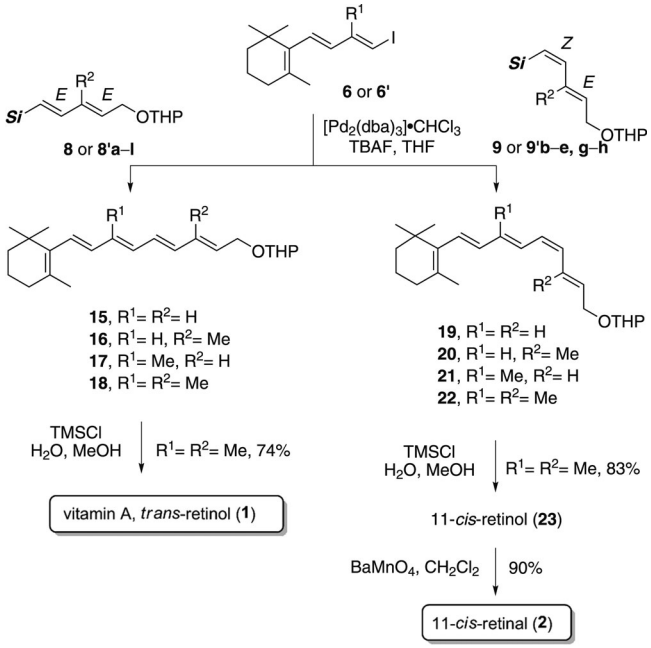
good yields by one or another of the methods described. Method A provided the complete collection of (1*E*,3*E*)-dienylsilanes except siletanes **8c** and **8′c**, which were prepared by method C. This latter method also afforded silanols **8b** and **8′b**, but no other silicon electrophiles were able to react under these conditions. Method B did not work under any of the conditions tested. Of the targeted (1*Z*,3*E*)-dienylsilanes, method D afforded the siletanes (**9c**, **9′c**) and the benzyl (**9d**, **9′d**), hydrosilyl (**9e**, **9′e**) and aryl/heteroaryl (**9g** and **9h**, and **9′g** and **9′h**) derivatives, but in all other cases we were unable to prepare the required alkynylsilane or to bring about its *cis* reduction. None of the other methods were able to produce (1*Z*,3*E*)-dienylsilanes.

The stereochemistry of the double bonds in compounds **8**, **8′**, **9** and **9′** was unambiguously deduced from the coupling constants (*J*) of their ^{1}H NMR spectra: values in the range of 13–15 Hz for the double bond of β-(*Z*)-isomers and 18–20 Hz for β-(*E*)-isomers were in good agreement with those reported in the literature.[25] Compared to the analogous dienylboronates and stannanes that have previously been used for retinoid synthesis by our group, the dienylsilanes used in this work are more stable, and could be chromatographed and otherwise handled without risk.[44]

Synthesis of all-*trans* and 11-*cis*-retinyl ethers: Hiyama cross-coupling reactions: After having prepared (1*E*,3*E*)-dienylsilanes **8a–l** and **8′a–l** and (1*Z*,3*E*)-dienylsilanes **9b–e**, **g** and **h** and **9′b–e**, **g** and **h**, we explored their palladium-catalysed cross-coupling to trienyl iodides **6** and **6′**[17c] (Table 4). Initial experiments were carried out under standard conditions by using fluoride-based activation.[45] Addition of tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 2–3 equiv) to a solution of the silane (1.5–2.5 equiv) in THF, followed by sequential addition of iodide and $[Pd_2(dba)_3]\cdot CHCl_3$ (0.05–0.1 equiv), cleanly afforded the corresponding retinyl ethers as pure isomers. All of the silanes except the phenyl derivatives[46] coupled efficiently under very mild conditions (0 °C or RT) and in short reaction times (10–30 min), regardless of their geometry (*E*/*Z*) and of steric congestion in the electrophile or the organosilicon compound. In the *E* series, both oxygen-activated silanes and "safety-catch" silanols gave excellent yields of the corresponding all-*trans*-retinyl ethers **15**–**18**, mostly in the range of 80–95 % (Table 4). In the *Z* series, yields were slightly lower (70–85 %) probably due to the instability of the corresponding 11-*cis*-retinyl ethers **19**–**22**. All yields were appreciably higher than those previously reported for the analogous Suzuki and Stille approaches.[11e,n,17c]

The activation of silanols can also be promoted by non-fluoride reagents that lack the drawbacks of fluoride reagents (corrosiveness, incompatibility with silicon protecting groups and the high cost of those that are soluble in organic solvents). The first such compound was silver(I) oxide, reported by Hiyama, Mori and co-workers.[47] Denmark and co-workers have extensively described the coupling of organosilanols either in the presence of Brønsted bases (including the inexpensive potassium trimethylsilanolate (KOTMS), which is soluble in organic solvents) or as their preformed silanolate salts.[48] In this work, fluoride-free coupling of iodide **6** to silanol **8b** was rather less efficient than fluoride-promoted coupling: retinyl ether **18** was obtained in 61 % yield under Ag_2O activation ($[Pd(PPh_3)_4]$, 50 °C, 8 h) and in 74 % yield under KOTMS activation ($[Pd_2(dba)_3]\cdot CHCl_3$, dioxane, 3 h, compared with 89 % with TBAF; Table 4).

Table 4. Hiyama cross-coupling reactions.



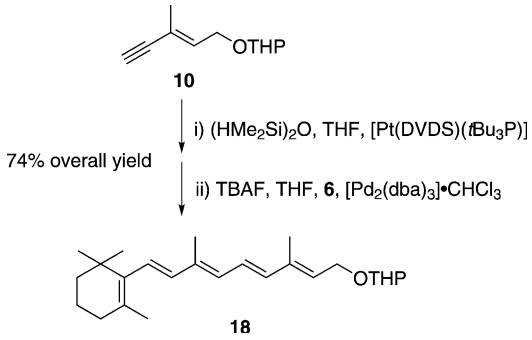
Entry	**8** or **8′**	*Si*	**15**	**16**	**17**	**18**
1	**a**	$Me_2(OEt)Si$	86	86	85	86
2	**b**	$Me_2(OH)Si$	88	72	89	89
3			–	–	–	61[a]
4			–	–	–	74[b]
5	**c**	$Me(CH_2)_3Si$	88	73	83	85
6	**d**	Me_2BnSi	79	73	80	77
7	**e**	$HiPr_2Si$	79	90	84	85
8	**f**	$Me_2allylSi$	82	79	93	82
9	**g**[c]	Me_2PhSi	–	–	–	–
10	**h**	$Me_2[3,5\text{-}(CF_3)_2]PhSi$	94	90	95	85
11	**i**	$Me_2$2-PySi	84	93	75	80
12	**j**	$Me_2$2-ThSi	88	79	83	80
13	**l**	$Me_2[2\text{-}(CH_2OH)Ph]Si$	–	–	–	70
14			–	–	–	35[d]
15			–	–	–	74[e]
Entry	**9** or **9′**	*Si*	**19**	**20**	**21**	**22**
16	**b**	$iPr_2(OH)Si$	82	79	77	71
17	**c**	$Me(CH_2)_3Si$	79	76	78	85
18	**d**	Me_2BnSi	70	76	76	78
19	**e**	$HiPr_2Si$	71	73	82	73
20	**g**	Me_2PhSi	–	–	–	–
21	**h**	$Me_2[3,5\text{-}(CF_3)_2]PhSi$	71	79	81	74

[a] Activation by Ag_2O ($[Pd(PPh_3)_4]$, THF, 50 °C). [b] Activation by KOTMS ($[Pd_2(dba)_3]\cdot CHCl_3$, dioxane). [c] No reaction under activation by TBAF or KOTMS. [d] Activation by KOTMS ($PdCl_2$, *N*-(2-diphenylphosphinobenzylidene)cyclohexylamine, DMSO). [e] One-pot procedure ($Me_2SiOSiMe_2$, [Pt(DVDS)(*t*Bu$_3$P)], **10**, THF; then, TBAF, $[Pd_2(dba)_3]\cdot CHCl_3$, **6**).

We also attempted non-fluoride coupling of [2-(hydroxylmethyl)phenyl]silanes, Hiyama, Nakao and co-workers[23] having reported that intramolecular coordination of the proximal hydroxyl group allows cross-coupling under conditions significantly milder than the standard, and that the metal residue (a cyclic silyl ether) can readily be recovered and reused. In this work, after attempts to couple **8l** with iodide **6** by using various bases (K_2CO_3, Cs_2CO_3), solvents (DMSO, THF) and catalysts ($PdCl_2$, $[Pd_2(dba)_3]$) had all led to the recovery of starting materials, activation with KOTMS ($PdCl_2$, *N*-(2-diphenylphosphinobenzylidene)cyclohexylamine, DMSO) afforded a poor 35% yield of **18** (Table 4).

Failure also met the use of triflate **7** as the electrophile in the cross-coupling reaction (data not shown). Neither fluoride-promoted protocols (TBAF, $[Pd(PPh_3)_4]$, THF,[49] or TBAF·3 H_2O, $PdBr_2$, (2-biphenyl)(tBu)$_2$P, dioxane[50]) nor the use of a slightly soluble Brønsted base promoter ($[Pd(dba)_2]$, X-Phos, K_3PO_4, dioxane)[51] achieved its coupling to silanol **8b**, the only products isolated from the reaction mixtures being starting materials.[52]

By contrast, synthesis of the retinoid skeleton by a sequential one-pot process combining the platinum-catalysed hydrosilylation of an alkyne with the palladium-catalysed Hiyama coupling was successful (Scheme 2).[53] Following



Scheme 2. One-pot hydrosilylation/cross-coupling sequence.

Denmark's protocol,[54] enyne **10** was hydrosilylated with inexpensive, non-toxic tetramethyldisiloxane under [Pt(DVDS)(tBu$_3$P)] catalysis, and the resulting vinyldisiloxane coupled in situ to iodide **6** under fluoride-promoted Pd catalysis, giving *trans*-*O*-tetrahydropyranyl retinyl ether **18** in a valuable 74% overall yield.

Finally, synthesis of the natural retinoids **1** and **2** was completed by deprotection of retinyl ethers **18** and **22** (TMSCl, H_2O, MeOH, 5 min), which afforded *trans*-retinol (**1**) and 11-*cis*-retinol (**23**) in 74 and 83% yield, respectively, followed by mild oxidation of **23** with $BaMnO_4$ (90%; Table 4).

Conclusion

The stereoselective synthesis of the highly conjugated skeleton of retinoids is a demanding and challenging task. In this paper, we have conclusively demonstrated that natural all-*trans*- and 11-*cis*-retinoids and their 9- and 13-demethylated analogues can be obtained by cross-coupling appropriate electrophiles with a wide variety of organo-functional dienylsilanes (both oxygen-activated species and "safety-catch" silanols) as a preferable alternative to classical borane or stannane coupling partners. The advantages of silicon-based coupling include the greater stability and lower toxicity of the dienylsilanes, the wide variety of substituents that can be placed on the silicon (which allows convenient choices of preparation and activation protocols), the need for only mild reaction conditions and uniformly high yields. These properties establish the Hiyama coupling approach as the most effective route to retinoids that has been reported to date.

Experimental Section

General: All of the solutions employed were degassed by argon bubbling over 15 min. Cross-coupling reactions and purification of retinoids were carried out in the absence of light.

General procedures for the synthesis of (1*E*,3*E*)-dienylsilanes 8 and 8′

Method A: Silane (H-***Si***) (1.0–1.5 equiv) was added dropwise to a solution of [Pt(DVDS)] (0.1 M in xylenes, 0.005 equiv) and tBu$_3$P (0.005 equiv) in THF (3 mL mmol^{-1}), and the mixture was stirred for 30 min at RT. A solution of (*E*)-3-methyl-5-(tetrahydropyran-2-yloxy)pent-3-en-1-yne (**10**) or (*E*)-5-(tetrahydropyran-2-yloxy)pent-3-en-1-yne (**10′**; 1.0 equiv) in THF or toluene was then added over 10 min and the reaction mixture was stirred for 1–10 h at RT or 100 °C. The solvent was removed under vacuum and the crude was purified by column chromatography to afford compounds **8a–l** or **8′a–l**, respectively.

Method B: $[Pd_2(dba)_3]$•CH_3Cl (0.015 equiv) was added to a solution of silane (H-***Si***; 1.0–1.5 equiv), KOAc (3.0 equiv), NMP (20 mL mmol^{-1}) and (1*E*,3*E*)-1-iodo-3-methyl-5-(tetrahydropyran-2-yloxy)penta-1,3-diene (**11**) or (1*E*,3*E*)-1-iodo-5-(tetrahydropyran-2-yloxy)penta-1,3-diene (**11′**; 1.0 equiv) and, after stirring for 1 h, the reaction was quenched with water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with water and brine. The organic layer was dried and filtered. This method did not afford the desired products in any of the cases tested.

Method C: nBuLi (2.5 M in hexanes, 1.3 equiv) was added over 10 min to a cooled solution (−78 °C) of (1*E*,3*E*)-1-iodo-3-methyl-5-(tetrahydropyran-2-yloxy)penta-1,3-diene (**11**) or (1*E*,3*E*)-1-iodo-5-(tetrahydropyran-2-yloxy)penta-1,3-diene (**11′**; 1 equiv) in diethyl ether (3 mL mmol^{-1}), and the reaction mixture was stirred at this temperature for 1 h. A solution of hexamethylcyclotrisiloxane or chloromethylsilacyclobutane (1.5 equiv) in diethyl ether (1 mL) was added at the same temperature and the reaction was allowed to warm to RT for 4–6 h. The solution was then cooled to 0 °C and quenched with water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with water and brine. The organic layer was dried and filtered. The solvent was evaporated and the crude was purified by column chromatography to afford compounds **8b–c** or **8′b–c**, respectively.

General procedure for the synthesis of alkynylsilanes 14 and 14′: nBuLi (1.3 equiv) was added over 10 min to a solution of (*E*)-3-methyl-5-(tetrahydropyran-2-yloxy)pent-3-en-1-yne (**10**) or (*E*)-5-(tetrahydropyran-2-yloxy)pent-3-en-1-yne (**10′**; 1.0 equiv) in diethyl ether cooled to −78 °C, and the reaction mixture was stirred at this temperature for 1 h. A solu-

tion of chlorosilane (***Si***-X; 1.5 equiv) in diethyl ether was added at the same temperature and the reaction was allowed to warm to RT for 4 h. The solution was then cooled to 0 °C and quenched with water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with water and brine. The organic layer was dried with anhydrous sodium sulphate and filtered. The solvent was evaporated and the crude was purified by column chromatography, to obtain compounds **14c–h** or **14′c–h**.

General procedure for the synthesis of (1*Z*,3*E*)-dienylsilanes 9 and 9′

Method D: A solution of alkynylsilanes **14c–h** or **14′c–h** (1 equiv) in THF was added dropwise to a stirred suspension of [ZrCl(Cp)$_2$(H)] (1.25–2.5 equiv) in THF and the mixture was stirred for 4 h until the hydrozirconation was complete, as shown by the disappearance of the insoluble hydride and the formation of a clear solution. It was then diluted with *n*-pentane (25 mL mmol^{-1}), stirred for a further 20 min, filtered through a short pad of neutral alumina and concentrated. Flash column chromatography of the crude afforded compounds **9c–e**, **g** and **h** or **9′c–e**, **g** and **h**.

General procedure for the Hiyama cross-coupling of organosilicon compounds 8 and 8′ and 9 and 9′ with trienyl iodides 6 and 6′ under TBAF activation: TBAF (1.0 M in THF, 2–3 equiv) was added dropwise to a solution of the organosilicon reagent (**8**, **8′**, **9** or **9′** (1.5–2.5 equiv) in THF (20 mL mmol^{-1}) and the mixture was stirred for 30 min (0 °C–RT). A solution of trienyl iodides **6** or **6′** (1.0 equiv) in THF and [Pd$_2$(dba)$_3$]·CHCl$_3$ (0.05–0.1 equiv) were sequentially added at RT, and the mixture was stirred for 1 h. Diethyl ether was added and the mixture was filtered through a short pad of silica gel. The solvent was removed under vacuum and the crude mixture was purified by column chromatography (SiO$_2$, 95:5 hexane/AcOEt) to afford the corresponding retinyl ethers (**15**–**22**) as yellow oils.

***trans*-Tetrahydropyran-2-yl retinyl ether (18)**

Siloxane coupling: By following the general procedure, treatment of a solution of siloxane **8a** (40 mg, 0.14 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 220 μL, 0.22 mmol), followed by addition of a solution of iodide **6** (30 mg, 0.095 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (5 mg, 0.005 mmol) afforded compound **18** in 86 % yield (30 mg).

Silanol coupling: By following the general procedure, reaction of a solution of silanol **8b** (68 mg, 0.26 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 190 μL, 0.19 mmol), followed by the addition of a solution of iodide **6** (35 mg, 0.11 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (6 mg, 0.006 mmol) afforded compound **18** in 89 % yield (36 mg).

Ag$_2$O activation: Silanol **8b** (63 mg, 0.24 mmol) and iodide **6** (39 mg, 0.12 mmol) were sequentially added to a suspension of [Pd(PPh$_3$)$_4$] (7 mg, 0.006 mmol) and Ag$_2$O (28 mg, 0.12 mmol) in THF (2 mL). The temperature was raised to 50 °C and the reaction mixture was stirred for 8 h, filtered through a pad of neutral alumina, concentrated and purified to afford compound **18** in 61 % yield (27 mg).

KOTMS activation: Silanol **8b** (36 mg, 0.15 mmol) was added to a stirred suspension of potassium trimethylsilanolate (25 mg, 0.19 mmol) in dioxane (2 mL) and the reaction mixture was stirred for 30 min. Iodide **6** (30 mg, 0.09 mmol) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (5 mg, 0.005 mmol) were then sequentially added and the mixture was stirred for 3 h, filtered through a pad of neutral alumina, concentrated and purified to afford compound **18** in 74 % yield (25 mg).

Silacyclobutane coupling: By following the general procedure, treatment of a solution of silacyclobutane **8c** (19 mg, 0.071 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 150 μL, 0.150 mmol) for 30 min at 0 °C, followed by addition of a solution of iodide **6** (15 mg, 0.048 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (3 mg, 0.003 mmol) afforded compound **18** in 85 % yield (15 mg).

Benzylsilane coupling: By following the general procedure, treatment of a solution of benzylsilane **8d** (31.6 mg, 0.096 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 128 μL, 0.128 mmol) for 30 min at 0 °C, followed by addition of a solution of iodide **6** (20 mg, 0.064 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (2 mg, 0.002 mmol) afforded compound **18** in 77 % yield (18 mg).

Silylhydride coupling: By following the general procedure, treatment of a solution of silylhydride **8e** (28 mg, 0.096 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 96 μL, 0.96 mmol) for 30 min at 0 °C, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (2 mg, 0.002 mmol) afforded compound **18** in 85 % yield (15 mg).

Allylsilane coupling: By following the general procedure, treatment of a solution of allylsilane **8f** (20 mg, 0.07 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 95 μL, 0.09 mmol) for 5 min at RT, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (1 mg, 0.001 mmol) afforded compound **18** in 82 % yield (14 mg).

3,5-Bis(trifluoromethyl)phenylsilane coupling: By following the general procedure, treatment of a solution of 3,5-bis(trifluoromethyl)phenylsilane **8h** (33 mg, 0.07 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 100 μL, 0.10 mmol) for 30 min at RT, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (3 mg, 0.003 mmol) afforded compound **18** in 85 % yield (15 mg).

Pyridylsilane coupling: By following the general procedure, treatment of a solution of pyridylsilane **8i** (22 mg, 0.07 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 150 μL, 0.15 mmol) for 30 min at 0 °C, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (3 mg, 0.003 mmol) afforded compound **18** in 80 % yield (14 mg).

Thiophenylsilane coupling: By following the general procedure, treatment of a solution of thiophenylsilane **8j** (23 mg, 0.07 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 190 μL, 0.19 mmol) for 5 min at RT, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (3 mg, 0.003 mmol) afforded compound **18** in 80 % yield (14 mg).

2-Hydroxymethylphenylsilane coupling: By following the general procedure, treatment of a solution of 2-hydroxymethylphenylsilane **8l** (22 mg, 0.07 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 100 μL, 0.10 mmol) for 5 min at RT, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (3 mg, 0.002 mmol) afforded compound **18** in 83 % yield (14 mg). With other activators like K$_2$CO$_3$ or Cs$_2$CO$_3$ the reaction did not take place and, with KOTMS, a 35 % yield (6 mg) was obtained.

One-pot reaction: 1,1,3,3-Tetramethyldisiloxane (31 mg, 0.237 mmol) was added dropwise to a solution of [Pt(DVDS)] (0.1 M in xylenes, 15 μL, 0.0015 mmol) and *t*Bu$_3$P (1 μL, 0.002 mmol) in THF (1 mL), and the mixture was stirred for 30 min. A solution of (*E*)-3-methyl-5-(tetrahydropyran-2-yloxy)pent-3-en-1-yne (**10**; 52 mg, 0.28 mmol) in THF (1 mL) was then added over 5 min and the reaction mixture was stirred for 30 min. TBAF (1.0 M in THF, 632 μL, 0.632 mmol), [Pd$_2$(dba)$_3$]·CHCl$_3$ (8 mg, 0.008 mmol) and iodide **6** (50 mg, 0.16 mmol) were then sequentially added and the reaction mixture was stirred, filtered through a pad of neutral alumina and concentrated. The crude was purified by column chromatography (SiO$_2$, 95:5 hexane/AcOEt) to afford compound **18** in 74 % overall yield (44 mg).

11-*cis*-Tetrahydropyran-2-yl retinyl ether (22)

Silanol coupling: By following the general procedure, treatment of a solution of silanol **9b** (22 mg, 0.07 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 95 μL, 0.10 mmol) for 30 min at 0 °C, followed by addition of a solution of the iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (1 mg, 0.001 mmol) afforded compound **22** in 71 % yield (12 mg).

Silacyclobutane coupling: By following the general procedure, treatment of a solution of silacyclobutane **9c** (21 mg, 0.08 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 189 μL, 0.189 mmol) for 30 min at 0 °C, followed by addition of a solution of the iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (4 mg, 0.004 mmol) afforded compound **22** in 85 % yield (15 mg).

Benzylsilane coupling: By following the general procedure, treatment of a solution of benzylsilane **9d** (80 mg, 0.242 mmol) in THF (5 mL) with TBAF (1.0 M in THF, 322 μL, 0.322 mmol) for 30 min at 0 °C, followed by addition of a solution of iodide **6** (50 mg, 0.16 mmol) in THF (1 mL) and

$[Pd_2(dba)_3]$·$CHCl_3$ (4 mg, 0.004 mmol) afforded compound **22** in 78% yield (36 mg).

Silylhydride coupling: By following the general procedure, treatment of a solution of silylhydride **9e** (28 mg, 0.10 mmol) in THF (5 mL) with TBAF (1.0 M in THF, 96 μL, 0.96 mmol) for 30 min at 0 °C, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and $[Pd_2(dba)_3]$·$CHCl_3$ (2 mg, 0.002 mmol) afforded compound **22** in 73% yield (13 mg).

3,5-Bis(trifluoromethyl)phenylsilane coupling: By following the general procedure, treatment of a solution of 3,5-bis(trifluoromethyl)phenylsilane **9h** (32 mg, 0.07 mmol) in THF (2 mL) with TBAF (1.0 M in THF, 100 μL, 0.10 mmol) for 30 min at 0 °C, followed by addition of a solution of iodide **6** (15 mg, 0.05 mmol) in THF (1 mL) and $[Pd_2(dba)_3]$·$CHCl_3$ (3 mg, 0.002 mmol) afforded compound **22** in 74% yield (13 mg).

***trans*-Retinol (Vitamin A, 1)**: Water (72 μL, 4.00 mmol) and trimethylsilyl chloride (50 μL, 0.39 mmol) were sequentially added to a solution of *trans*-tetrahydropyran-2-yl retinyl ether (**18**; 25 mg, 0.07 mmol) in MeOH (3 mL), and the reaction was stirred open to air for 10 min. A saturated aqueous solution of $NaHCO_3$ (10 mL) was then added and the aqueous phase was extracted with diethyl ether (2×15 mL). The combined organic layers were washed with water (2×15 mL) and brine (2×15 mL), dried with (anhydrous) sodium sulphate and filtered. The solvent was evaporated and the crude was purified by column chromatography (SiO_2, 80:20 hexane/AcOEt) to yield compound **1** (14 mg, 74%) as a yellow oil.

11-*cis*-Retinol (23): By following the same procedure as described for compound **1**, treatment of a solution of 11-*cis*-tetrahydropyran-2-yl retinyl ether (**22**; 15 mg, 0.04 mmol) in MeOH (2 mL) with water (50 μL, 2.77 mmol) and trimethysilyl chloride (30 μL, 0.24 mmol) for 10 min afforded, after column chromatography (SiO_2, 80:20 hexane/AcOEt), compound **23** (9.5 mg, 83%) as a yellow oil.

11-*cis*-Retinal (2): A solution of 11-*cis*-retinol (**23**; 10 mg, 0.03 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a suspension of $BaMnO_4$ (28 mg, 0.11 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred for 6 h, filtered through a short pad of neutral alumina (IV, hexane) and concentrated. Flash column chromatography of the crude (Al_2O_3, hexane) afforded 11-*cis*-retinal (**2**) as an unstable yellow oil (9 mg, 90% yield).

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