Bidirectional Hiyama-Denmark Cross-Coupling Reactions of Bissilyldeca-1,3,5,7,9-pentaenes for the Synthesis of Symmetrical and Non-symmetrical Carotenoids

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Summary: The construction of the carotenoid skeleton by Pd-catalyzed Csp^2-Csp^2 cross-coupling reactions of symmetrical and non-symmetrical 1,10-bissilyldeca-1,3,5,7,9-pentaenes and the corresponding complementary alkenyl iodides has been developed. Reaction conditions for these bidirectional Hiyama-Denmark cross-coupling reactions of bis-functionalized pentaenes are mild and the carotenoid products preserve the sterochemical information of the corresponding oligoene partners. The carotenoids synthesized in this manner include β,β-carotene and (3*R*,3´*R*)-zeaxanthin (symmetrical) as well as 9-*cis*-β,β-carotene, 7,8-dihydro-β,β-carotene and β-cryptoxanthin (non-symmetrical).

Introduction

Polyene substructures are present in a large number of molecular skeletons of natural products that display diverse biological activities.{Thirsk, 2002 #1749;Madden, 2014 #4305} Notably, the polyene fragments of retinoids and carotenoids are considered to be responsible for some fundamental biological functions, including animal vision (11-*cis*-retinal) and bacterial proton- and ion-pumping activities (all-*trans*-retinal),{Wald, 1934 #1893;Palczewski, 2006 #992;Hofmann, 2009 #1169;Palczewski, 2012 #1736} and plant photosynthesis (carotenoids){Britton, 2004 #1763;Laudrum, 2010 #1582} among others.{Blomhoff, 1994 #2722;Nau, 1999 #2724;Livrea, 2000 #2725;Preedy, 2012 #2532} More than 800 known natural carotenoids have been isolated from Nature,{Britton, 1995 #1760;Britton, 1995 #1761;Britton, 2004 #1763} with a large number of them still remaining incompletely characterized due to their instability or to the scarcity of material isolated from the natural sources.

Csp^2=Csp^2 condensation reactions (Wittig, Horner-Wadsworth-Emmons or HWE, Julia-Kocienski...) are considered as classical methods{Nicolaou, 1997 #1657;Nicolaou, 2005 #682} for the synthesis of the polyene substructures of retinoids and carotenoids.{Alvarez, 2014 #3362} Despite their efficiency, these procedures have some drawbacks, notably the lack of stereocontrol leading to mixtures of isomers, and a laborious purification requiring also the separation of by-products.{Alvarez, 2014 #3362} Alternatively these polyenes are constructed using palladium-catalyzed Csp^2-Csp^2 cross-coupling reactions. These processes are more functional group-tolerant and require in general milder reaction conditions, thus leading to the preservation of the stereochemical information of the reacting oligoenes.{Alvarez, 2014 #3362;Nicolaou, 2005 #682}

Both the Stille{Stille, 1986 #4236;Espinet, 2004 #1790;Heravi, 2014 #3184} and the Suzuki-Miyaura cross-coupling reactions{Miyaura, 1995 #1518;Suzuki, 2005 #3177;Suzuki, 2011 #1791} have been thoroughly explored for the synthesis of apocarotenoids (including the retinoids or vitamin A analogues) and carotenoids{Olpp, 2006 #1588;Burghart, 2008 #1590;Vaz, 2007 #1630;Vaz, 2013 #3164} using mono- and bis-functionalized alkenyl linchpins.{Cornil, 2015 #3437} In fact, these synthetic challenges have contributed to illustrate the scope and limitations of the Pd-catalyzed Csp^2-Csp^2 cross-coupling reactions for the preparation of highly unstable polyenes.{Alvarez, 2014 #3362} As a result, some drawbacks have been identified,{Nicolaou, 2005#682;Johansson Seechurn, 2012 #1989;de Meijere, 2014 #3489} which are primarily related to the particular nature of the organometallic donors, such as homodimerization in the case of organotin reagents in Stille couplings, and protiodeborylation of organoboranes in Suzuki couplings. With partners that exhibit low reactivity some erosion on the *E/Z* selectivity has also been detected.{Lu, 2012 #1808}

Similarly, the Hiyama-Denmark cross-coupling reaction,{Hiyama, 1998 #4235;Denmark, 2004 #4297;Sore, 2012 #3524} which utilizes organosilicon reagents,{Becerra, 1998 #4239} has also been applied to the stereocontrolled synthesis of the all-*trans*- and 11-*cis*-isomers of vitamin A by the highly convergent C_{14} + C_6 strategy.{Alvarez, 2014 #3362} For example, dienylsilane **2** was found to couple to trienyliodide **1** under mild reaction conditions to afford the retinoid pentaene structure **3** in high yield (Scheme 1).{Montenegro, 2008 #1990;Montenegro, 2009 #2097;Bergueiro, 2012 #1798} Organosilicon reagent are in general easier to prepare and handle than structurally related organometallic compounds. In addition, they are also more stable due

to the low polarizability of the C-Si bond, and show lower toxicity than stannanes. Moreover, mechanistic studies have provided an in-depth understanding of the cross-coupling reaction{Denmark, 2009 #1999;Denmark, 2004 #4285;Denmark, 2004 #4284;Denmark, 2006 #3557;Denmark, 2008 #1998;Amatore, 2014 #4317;Tymonko, 2015 #4288;Tymonko, 2015 #4289}, including the effect of silicon substituents on their reactivity{Denmark, 2006 #4292;Denmark, 2015 #4295} and the electronic demands for efficient transmetalation.{Denmark, 2011 #4293} All of these features have contributed to the current status of organosilanes as powerful synthetic tools for the preparation of unsaturated fragments of natural polyenes.{Hatanaka, 1991 #4313;Hiyama, 1994 #4278;Denmark, 2002 #431;Denmark, 2004 #1994;Nakao, 2006 #4337;Denmark, 2006 #1996;Denmark, 2008 #1998;Denmark, 2009 #1999;Denmark, 2010 #1995;Nakao, 2011 #2455;Sore, 2012 #3524}

A popular strategy in the construction of the polyene skeleton of carotenoids involves connecting a central C12-pentaenyl fragment to two C14 end groups, the so-called C_{14} + C_{12} + C_{14} strategy (Scheme 1).{Alvarez, 2014 #3362} The application of the Hiyama-Denmark transform in this strategy would imply the generation of both the C11-C12 and the C11'-C12' bonds of carotenoids by using bis-metallated organosilanes **5-6** and alkenyliodides (such as **1**, for example).

In order for this bidirectional strategy using bismetallated organometallic reagents to be of general application, it would have to be able to provide access to both symmetrical (**7-8**) and non-symmetrical (**9-11**) polyene structures (Scheme 1), implying that selective activation of each of the metallic fragments associated to the central pentaene central core (as in **5-6**) is needed.

Denmark has already demonstrated that, while both of types of silyl groups are activated using fluoride anion sources through the formation of pentavalent Si species,{Denmark, 2000 #4332;Denmark, 2000 #4333;Denmark, 2004 #4285;Denmark, 2004 #4284} the treatment of silanols under basic conditions provides a second alternative pathway for activation via generation of active silanolate species.{Denmark, 2008 #4329} He has also taken advantage of this dual behavior in the bidirectional preparation of simple non-symmetrical bisarylbutadienes, hexatrienes and octatetraenes, devoid of substitution at the diene or tetraene moieties, using mixed silanol-silane 1,4-bissilylbutadienes.{Denmark, 2005 #4286;Denmark, 2005 #4314}review see{Denmark, 2010 #4296} However, the preparation/use of higher analogues of these bissilyl reagents has not been reported, while literature reports on other alkenyl bissilanes appear to be

restricted to the synthesis of symmetrical unsubstituted butadienyl-, hexatrienyl-,{Babudri, 1991 #4281} and octatetraenyl-bissilanes,{Babudri, 1997 #4282;Babudri, 1998 #4283} and their related use in mono- and bis-acylation reaction with aroyl chlorides.

With these precedents, in this paper we describe the preparation of pentaenyl-bissilane reagents **5** and **6**, and their application to the synthesis of both symmetrical (β β-carotene **7**, (3*R*,3′*R*)-zeaxanthin **8**) and non-symmetrical (9-*cis*-β-carotene **9**, 7,8-dihydro-β-carotene **10** and (*R*)-β-cryptoxanthin **11**) carotenoids (Scheme 1). To further add to the attractiveness of this strategy, it is noted that the oligoene skeleton that comprises the central region of carotenoids (integrated in structures **7-11**) is biosynthetically preserved in most of these natural products, while structural modifications (in the form of changes in oxidation state, ring contractions, etc ...) are found at the ring carbons and/or at their more proximal double bonds.{Britton, 1995 #1760;Britton, 1995 #1761;Britton, 2004 #1763} This makes the use of reagents **5** and **6** potentially useful for the synthesis of a wide variety of carotenoid structures.

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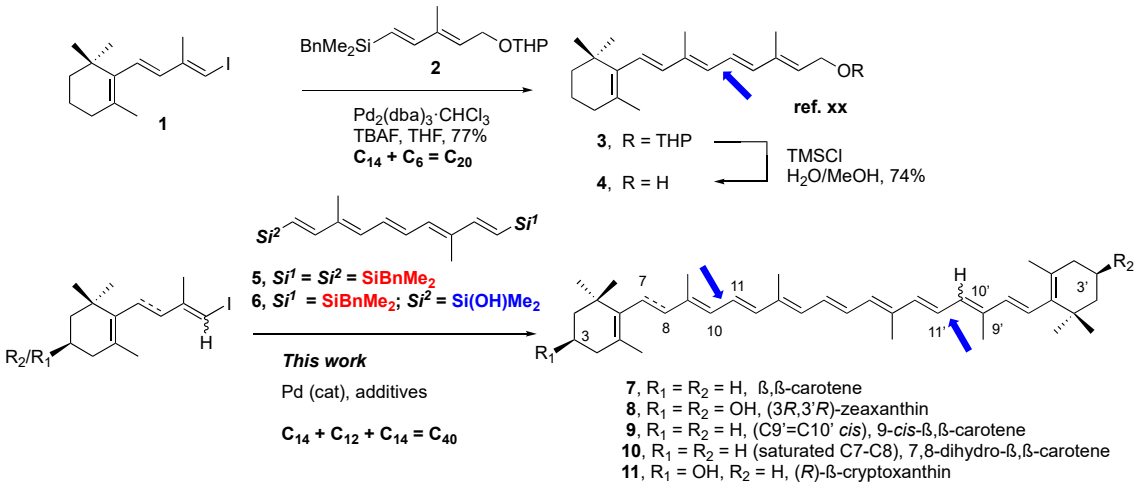


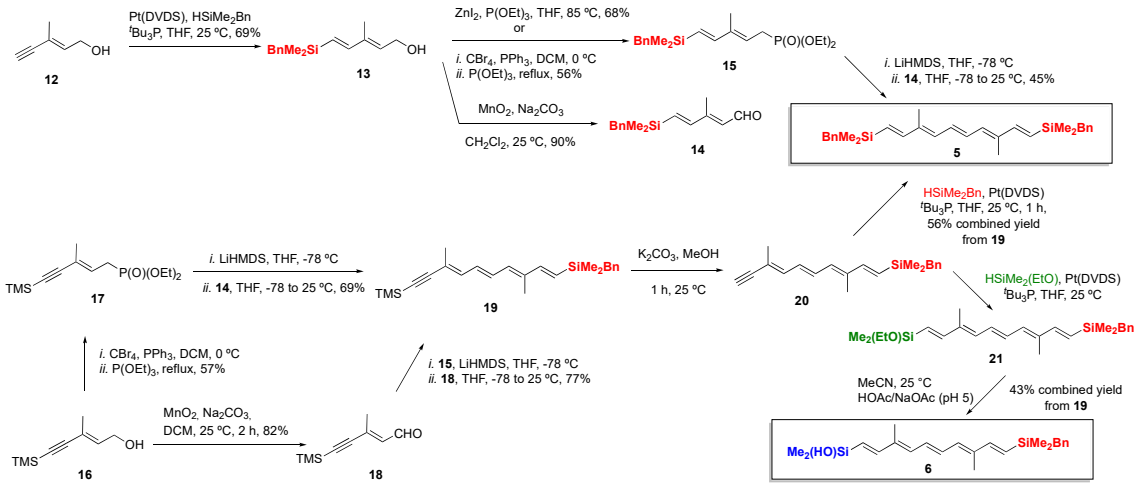
Scheme 1. Reported synthetic approach to vitamin A (**4**){Montenegro, 2008 #1990;Montenegro, 2009 #2097} and extension to β,β-carotene (**7**), (3*R*,3′*R*)-zeaxanthin (**8**), 9-*cis*-β-carotene (**9**), 7,8-dihydro-β-carotene (**10**) and (*R*)-β-cryptoxanthin (**11**) using a bi-directional Hiyama-Denmark cross-coupling reactions with symmetrical (**5**) and non-symmetrical (**6**) 1,10-bissilyldeca-1,3,5,7,9-pentaenes. ref. xx

Results and Discussion

Synthesis of 1,10-bissilyldeca-1,3,5,7,9-pentaenes 5 and 6

Starting from either **12** or TMS-substituted derivative **16** (Scheme 2), two routes were employed that differed in the order of hydrosilylation{Chandra, 1987 #4237;Lewis, 1991 #4240;Kyoko, 1993 #4335;Denmark, 2001 #4230;Trost, 2005 #4315;Roy, 2007

#4321;Marciniec, 2017 #4322} relative to oxidation{Dhulut, 2007 #4299} and HWE{Hoffmann, 2001 #2305;Byrne, 2013 #3148} steps. The first route started with a regioselective Pt-catalyzed Markovnikov *syn*-hydrosilylation{Chandra, 1987 #4237;Lewis, 1991 #4240;Kyoko, 1993 #4335;Denmark, 2001 #4230;Trost, 2005 #4315;Roy, 2007 #4321;Marciniec, 2017 #4322} of enynol **12** with $HSiMe_2Bn$ and Karstedt's catalyst [(tBu$_3$P)Pt(DVDS), (DVDS = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane, generated from Pt(DVDS) and tBu$_3$P] was highly regio- and stereoselective and afforded the corresponding silyldienol **13** in 69% yield.{Bergueiro, 2012 #1798} Oxidation of silyldienol **13** with MnO_2 afforded silyldienal **14** in 90% yield.{Dhulut, 2007 #4299} Allylic phosphonate **15** was prepared from **13** by reaction with triethylphosphite{Motozaki, 2005 #4324} of the corresponding iodide{Barney, 2011 #2561} or bromide{Barluenga, 2004 #4300} intermediates in 68% and 56% overall yields, respectively. Finally, unsaturated chain extension of silyldienal **14** by HWE reaction with phosphonate **15** under Barbier conditions afforded the symmetrical 3,8-dimethyl-1,10-bissilyl-1,3,5,7,9-decapentaene **5** in 45% yield.



Scheme 2. Synthesis of symmetrical (**5**) and non-symmetrical (**6**) pentaenylbissilanes from enynols **12** and **16**.

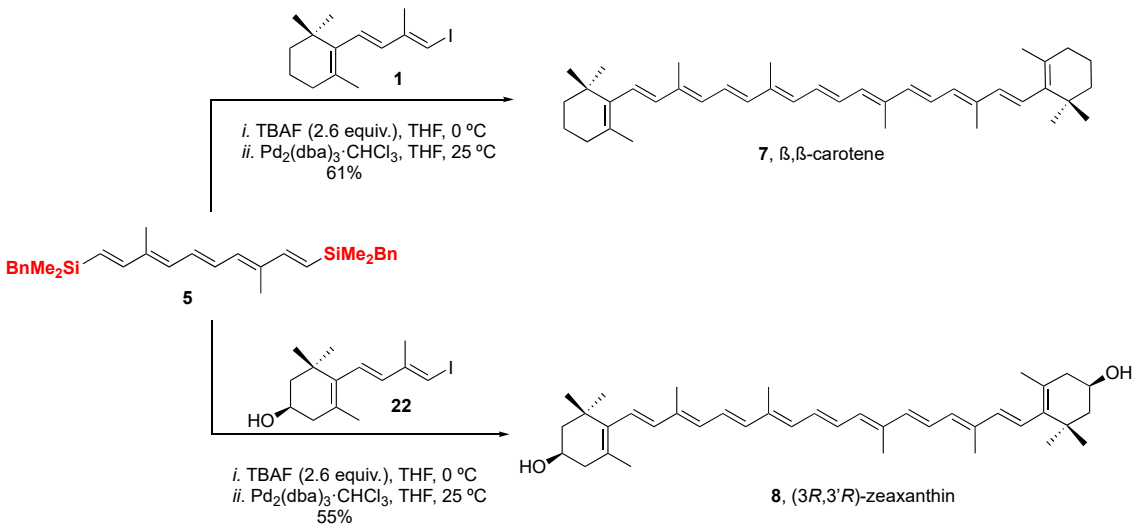
A more efficient approach (Scheme 2) to both **5** and the non-symmetrical 1,10-bissilyl-1,3,5,7,9-decapentaene **6** was devised involving tetraenynylsilane **20** as intermediate. Thus, TMS-enynol **16**, itself obtained by reduction of the corresponding enynoate precursor,{Trost, 1997 #195} was transformed into allylic phosphonate **17** along the same lines indicated for **15**,{Barluenga, 2004 #4300} and the subsequent HWE reaction with silyldienal **14** gave rise to tetraenynyl derivative **19** in 69% yield. A better yield (77%) resulted from the exchange of the functionalities between the reaction partners, thus

performing the HWE process between enynal **18** and phosphonate **15**.{Dhulut, 2007 #4299} Then, regio- and stereoselective Pt-catalyzed hydrosilylation{Chandra, 1987 #4237;Lewis, 1991 #4240;Denmark, 2001 #4230} of desilylated **20** with $HSiMe_2Bn$ or $HSi(OEt)Me_2$ and Karstedt's catalyst, afforded 1,10-bissilyldeca-1,3,5,7,9-pentaenes **5** and **21** in 56% and 88% overall yields from **19** (three steps from **19**), respectively. Alternatively, upon stirring crude **21** in aqueous buffer (1M HOAc/NaOAc, pH 5),{Denmark, 2005 #4286} the corresponding silanol **6** was obtained in an overall 43% yield from **19** (Scheme 2).{Denmark, 2005 #4286}

The all-*E* geometry of pentaenes **5** and **6** was assigned based on the magnitude of the C_{sp2}-H-C_{sp2}-H vicinal coupling constants (J = 18 – 20 Hz) on their ^{1}H NMR spectra{Faller, 2002 #4238} and the observed nuclear Overhauser effects (nOe).

Bidirectional Hiyama-Denmark cross-coupling of 1,10-bissilyldeca-1,3,5,7,9-pentaenes 5 and 6

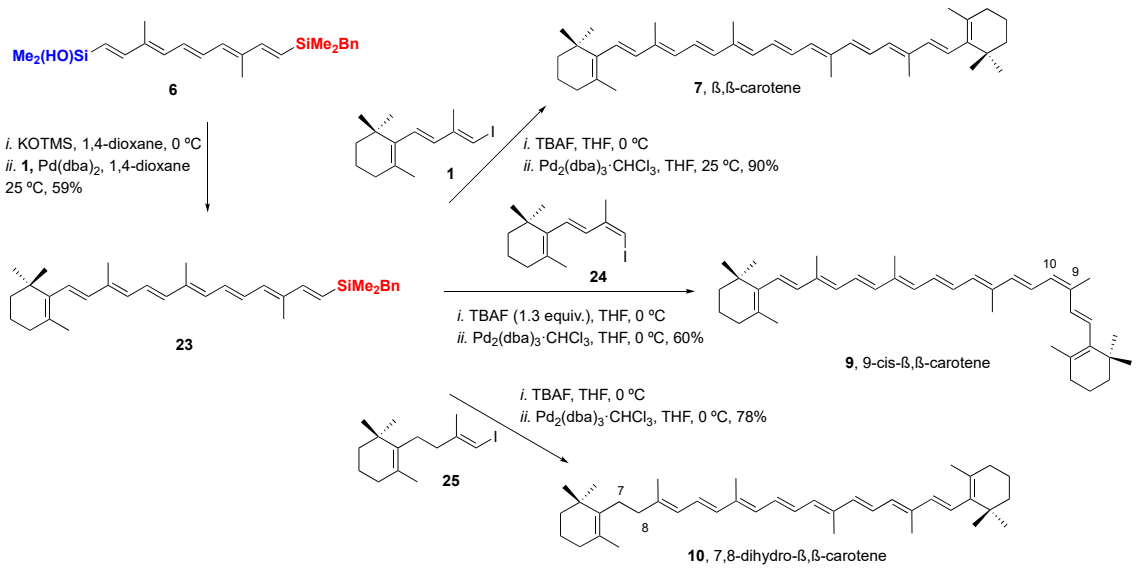
The two-fold bidirectional Hiyama-Denmark cross-coupling reaction{Hiyama, 1983 #4231;Nakao, 2011 #2748} using the homodimeric 1,10-bissilyldeca-1,3,5,7,9-pentaene **5** was performed following the protocol previously described for the synthesis of retinoids.{Bergueiro, 2012 #1798} Upon treatment with *n*Bu_4NF {Trost, 2001 #4242;Trost, 2003 #4232;Trost, 2005 #4243} in the presence of $Pd_2dba_3 \cdot CHCl_3$ as catalyst, the coupling of **5** with trienyliodide **1**{Vaz, 2002 #1629} took place at ambient temperature and afforded β,β-carotene **7** in 61% yield (Scheme 3). Similarly, (3*R*,3′*R*)-zeaxanthin **8** was also synthesized, in 55% yield, upon two-fold Hiyama-Denmark cross-coupling of **5** and trienyliodide **22**,{Vaz, 2002 #1629} thus showing the compatibility of the unprotected hydroxyl group with the reaction conditions. For the synthesis of zeaxanthin racemate{Isler, 1957 #4304}



Scheme 3. Total synthesis of symmetrical carotenoids (**5**, **8**) by Hiyama-Denmark cross-coupling of symmetrical pentaenylbissilane (**5**) and trienyliodides (**1** and **22**).

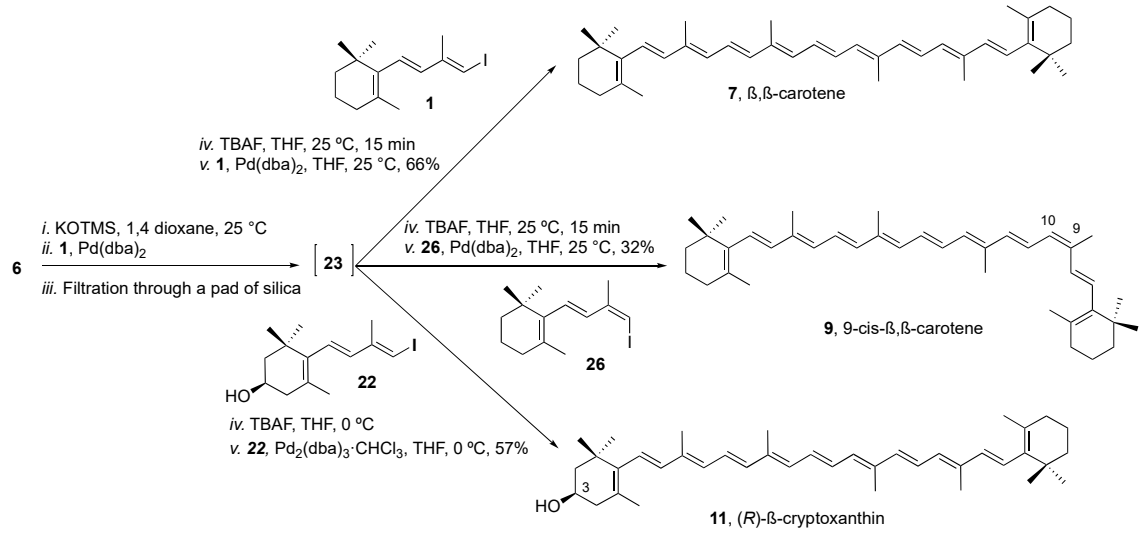
In order to explore the sequential Hiyama-Denmark cross-coupling{Denmark, 2001 #4230} of a non-symmetrical 1,10-bissilyldeca-1,3,5,7,9-pentaene with modulated reactivity,{Denmark, 2005 #4286} the silanol group of pentaenylbissilane **6** was selectively activated by treatment with KOTMS. Then, addition of $Pd(dba)_2$ and trienyliodide **1** afforded, at ambient temperature, octaenylsilane **23** with good efficiency (59 yield; Scheme 4). For the synthesis and characterization of the longest (10 and 14 conjugated double bonds) polyenyltriethoxysilane, see {Effenberger, 2001 #4336} Thus, the reactivity of the non-symmetrical 1,10-bissilyldeca-1,3,5,7,9-pentaene follows the same trends described for the shorter unsubstituted 1,4-bissilylbutadienes,{Denmark, 2005 #4286} and the observed selectivity can be diverted to the preparation of non-symmetrical carotenoids. This is clearly another advantage of the Hiyama-Denmark coupling for stepwise polyene construction.

Further coupling of octaenylsilane **23** with trienyliodide **1** or its *Z*-isomer **24** (Scheme 4) took place following activation with *n*Bu_4NF and using $Pd_2dba_3·CHCl_3$ as catalyst. This afforded, in 90% and 60% yields respectively, β,β-carotene **5** and the highly unstable 9-*cis* isomer **9**.{Bernhard, 1991 #2151;Yamano, 1999 #3532;Sher, 2018 #4150} Thus, the geometry of the starting trienyliodides appears to be preserved in the Hiyama-Denmark reaction. Similarly, 7,8-dihydro-β,β-carotene **10** could be obtained in 78% yield when the isolated octaenylsilane intermediate **23** was subjected to a second Hiyama-Denmark cross-coupling with the non-conjugated dienyliodide **25**, upon activation with TBAF using $Pd_2dba_3·CHCl_3$ as catalyst. This carotenoid has been isolated from the extracts of genetically-modified *E. coli*.{Takaichi, 1996 #1804}



Scheme 4. Synthesis of silylated octaenylapocarotenoid **23** by position-selective mono-Hiyama-Denmark cross-coupling of non-symmetrical 1,10-bissilyldecapentaene **6** and trienyliodide **1**, and synthesis of symmetrical (β,β-carotene **7**) and non-symmetrical (9-*cis*-β,β-carotene **9** and 7,8-dihydro-β,β-carotene **10**) by Hiyama-Denmark cross-coupling of octaenylsilane **23**.

Additionally, the bis-coupling process could be carried out without isolation of the octaenylsilane intermediate **23**. Thus, heterodimeric 1,10-bissilyldecapentaene **6** was also converted into β,β-carotene **7**, 9-*cis*-β,β-carotene **9**,{Bernhard, 1991 #2151;Yamano, 1999 #3532;Sher, 2018 #4150} and (*R*)-β-cryptoxanthin **11**{Khachik, 2007 #2609} (for a former total synthesis of the racemate, see:{Isler, 1957 #4304;Loeber, 1971 #4339}) in 66%, 30% and 57% yield, respectively, in a sequential double Hiyama-Denmark reaction of **6** with trienyliodides **1**, **26** and **22** (Scheme 5). This protocol involved first a Hiyama-Denmark coupling with *E*-trienyliodide **1** at the silanol terminus of **6**{Denmark, 2005 #4286;Denmark, 2001 #4334;Denmark, 2008 #4329} followed, after filtration of the crude mixture through a silica gel plug, by a second coupling{Trost, 2001 #4242;Trost, 2003 #4232;Trost, 2005 #4243} between the putative octaenylsilane intermediate **23** and trienyliodides **1**, **26** or **22**, respectively.



Scheme 5. Synthesis of symmetrical (β,β-carotene **7**) and non-symmetrical (9-*cis*-β,β-carotene **9**; (*R*)-β-cryptoxanthin **11**) by sequential selective mono-Hiyama-Denmark cross-coupling of non-symmetrical 1,10-bissilyldecapentaene **6**.

To summarize, as an extension of the Hiyama-Denmark cross-coupling approach{Denmark, 2009 #1999;Denmark, 2010 #1995;Nakao, 2011 #2748} to polyenes, we have developed a new synthesis of symmetrical and non-symmetrical carotenoids by bidirectional Pd-catalyzed Csp^2-Csp^2 bond formation using conjunctive pentaenyl-1,10-bissilanes and the apropriately matched (tri)enyl iodide building blocks. Conceptually, the application of transition metal catalyzed processes{de Meijere, 2004 #915} to carotenoids complements the general condensation approaches based on olefination, with the construction of polyenes by single-bond formation between unsaturated carbons.{Alvarez, 2014 #3362} These procedures are mild (ambient temperature) and functional group (OH) tolerant and the synthesis of the desired isomer can be achieved by choosing the geometries of the alkenyl reactants, since the oligoene products preserve the stereochemical information of the cross-coupling partners.{Thirsk, 2002 #1749} The stability of cross-coupling organosilane reagents, the cost-effectiveness and low environmental impact of their preparation are additional advantages of these protocols, particularly when used as tandem processes to more efficiently generate molecular complexity. In the case at hand, it is expected that using these procedures the synthesis of unstable (as exemplified by **9**) natural carotenoids will allow their full characterization and provide samples for comprehensive biological studies.

Acknowledgements

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GENERAL PROCEDURES

Solvents were dried according to published methods and distilled before use. All other reagents were commercial compounds of the highest purity available. Unless otherwise indicated all reactions were carried out under argon atmosphere, and those not involving aqueous reagents were carried out in oven-dried glassware. Analytical thin layer chromatography (TLC) was performed on aluminum plates with Merck Kieselgel 60F254 and visualized by UV irradiation (254 nm) or by staining with an ethanolic solution of phosphomolibdic acid. Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) C18-SiO2 and CN-SiO2 under pressure. Electron impact (EI) mass spectra were obtained on a Hewlett-Packard HP59970 instrument operating at 70 eV. Alternatively an APEX III FT-ICR MS (Bruker Daltonics), equipped with a 7T actively shielded magnet was used and ions were generated using an Apollo API electrospray ionization (ESI) source, with a voltage between 1800 and 2200 V (to optimize ionization efficiency) applied to the needle, and a counter voltage of 450 V applied to the capillary. For ESI spectra samples were prepared by adding a spray solution of 70:29.9:0.1 (v/v/v) CH_3OH/water/formic acid to a solution of the sample at a v/v ratio of 1 to 5% to give the best signal-to-noise ratio. High Resolution mass spectra were taken on a VG Autospec instrument. ^1H NMR spectra were recorded in C_6D_6 and acetone-d_6 at ambient temperature on a Bruker AMX-400 spectrometer at 400 MHz with residual protic solvent as the internal reference.

Diethyl (2*E*-4*E*)-5-(Benzyldimethylsilyl)-3-methylpenta-2,4-dienylphosphonate (15).

Method A: A solution of **13**{Bergueiro, 2012 #1977} (0.40 g, 1.62 mmol) in THF (6.5 mL) was added to a mixture of ZnI_2 (0.78 g, 2.44 mmol) and $P(OEt)_3$ (0.84 mL, 4.87 mmol). The reaction mixture was stirred for 4 h at 85 °C. After cooling down to 25 °C, the solvent was removed, the residue was washed with a 2 M solution of NaOH and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (C18 - silica gel, 55:45 v/v CH_3CN/H_2O) to afford 0.42 g (68%) of **15** as a yellow oil.

Method B: To a cooled (0 °C) stirred solution of **13**{Bergueiro, 2012 #1977} (0.30 g, 1.22 mmol) in CH_2Cl_2 (4 mL) were added CBr_4 (0.53 g, 1.58 mmol) and PPh_3 (0.48 g, 1.83 mmol). The reaction mixture was stirred for 15 min at 0 °C and the solvent was concentrated in *vacuo*. The residue was dissolved in $P(OEt)_3$ (0.29 mL, 1.79 mmol) and the mixture was refluxed for 30

min. After being cooled down to ambient temperature, toluene (1 mL) was added and the mixture was concentrated. The residue was purified by column chromatography (C18 - silica gel, 55:45 v/v CH_3CN/H_2O) to afford 0.25 g (56%) of **15** as a yellow oil. **^{1}H-NMR** (400.13 MHz, C_6D_6): δ 7.44 -7.20 (m, 2H, ArH), 7.01 (t, *J* = 6.9 Hz, 1H, ArH), 6.97 (d, *J* = 8.0 Hz, 2H, ArH), 6.64 (d, *J* = 19.0 Hz, 1H, H_4 or H_5), 5.80 (d, *J* = 19.0 Hz, 1H, H_5 or H_4), 5.73 – 5.63 (m, 1H, H_2), 3.98 – 3.82 (m, 4H, 2xO$\underline{CH_2}CH_3$), 2.57 (dd, *J* = 8.0 Hz, J_{HP} = 23.0 Hz, 2H, $2H_1$), 2.06 (s, 2H, $SiMe_2\underline{CH_2}Ph$), 1.68 (d, *J* = 3.9 Hz, 3H, C_3-CH_3), 1.02 (t, *J* = 7.1 Hz, 6H, 2xO$CH_2\underline{CH_3}$), 0.05 (s, 6H, $Si\underline{Me_2}Bn$) ppm. **^{13}C-NMR** (101.11 MHz, C_6D_6): δ 149.3 (d, $^4J_{C\text{-}P}$ = 5.0 Hz), 140.2 (s), 139.1 (s, $^3J_{C\text{-}P}$ = 14.5 Hz), 128.6 (d, 2x), 128.5 (d, 2x), 125.2 (d), 124.5 (d), 122.9 (d, $^2J_{C\text{-}P}$ = 12.2 Hz), 61.7 (t, 2x), 27.7 (t, $^1J_{C\text{-}P}$ = 139.6 Hz), 26.3 (t), 16.5 (q, 2x), 12.1 (q), -3.2 (q, 2x) ppm. **IR** (NaCl): υ 2982 (s, C-H), 2957 (m, C-H), 1492 (w), 1250 (s), 1027 (s) cm^{-1}. **HRMS** (EI^+): Cald. for $C_{19}H_{32}O_3PSi$ ($[M+H]^+$), 367.1853; found, 367.1856.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)-3-methylpenta-2,4-dienal (14). To a cooled (0 °C) solution of **13**{Bergueiro, 2012 #1798} (2.3 g, 9.33 mmol) in Et_2O (373 mL), MnO_2 (8.11 g, 93.34 mmol) and Na_2CO_3 (9.89 g, 93.34 mmol) were added and the reaction was stirred at 25 °C for 1.5 h. The mixture was filtered through Celite®, the solids were washed with CH_2Cl_2, and the solvent was evaporated to afford 2.05 g (89%) of **14** as a yellow oil. **^{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, $SiMe_2\underline{CH_2}Ph$), 1.65 (s, 3H, C_3-CH_3), -0.01 (s, 6H, $Si\underline{Me_2}Bn$) 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, 2x), 128.5 (d, 2x), 124.8 (d), 25.8 (t), 12.0 (q), -3.6 (q, 2x) ppm. **UV** (MeOH): λ_{max} 274 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.

Diethyl (*E*)-(3-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)phosphonate (17). To a cooled (0 °C) stirred solution of **16**{Trost, 1997 #195} (0.398 g, 2.365 mmol) in CH_2Cl_2 were added CBr_4 (1.02 g, 3.075 mmol) and PPh_3 (0.931 g, 3.548 mmol). The reaction mixture was stirred for 15 min at 0 °C and the solvent was evaporated. The residue was dissolved in triethylphosphite (0.56 mL, 3.005 mmol) and the resulting mixture was refluxed at 130 °C for 30 min. After being cooled down to room temperature, toluene (1 mL) was added and the mixture was concentrated. The residue was purified by column chromatography (C18 - silica gel, 55:45 v/v CH_3CN/H_2O) to afford 0.29 g (57%) of **187** as a yellow oil. **^{1}H-NMR** (400.13 MHz, C_6D_6): δ 6.17 – 6.09 (m, 1H, H_2), 3.91 – 3.78 (m, 4H, $PO(O\underline{CH_2}CH_3)_2$), 2.38 (dd, $J_{H\text{-}H}$ = 8.6 Hz, $^1J_{P\text{-}H}$ = 23.5 Hz, 2H, $2H_1$), 1.73 (d, $^5J_{H\text{-}P}$ = 5.1 Hz, 3H, C_3-CH_3), 0.97 (t, *J* = 7.1 Hz, 6H, $PO(OCH_2\underline{CH_3})_2$), 0.18 (s, 9H, $Si\underline{Me_3}$) ppm. **^{13}C-NMR** (100.16 MHz, C_6D_6): δ 128.1 (d, $^2J_{C\text{-}P}$ = 12.1 Hz), 122.3 (s, $^3J_{C\text{-}P}$ = 15.2 Hz),

108.4 (s, $^{4}J_{C\text{-}P}$ = 5.9 Hz), 91.9 (s, $^{5}J_{C\text{-}P}$ = 2.9 Hz), 61.7 (t), 61.6 (t), 27.8 (t, $^{1}J_{C\text{-}P}$ = 139.7 Hz), 17.5 (q $^{4}J_{C\text{-}P}$ = 5.6 Hz), 16.5 (q), 16.4 (q), 0.1 (q, 3x) ppm. **IR** (NaCl): ν 2966 (m, C-H), 2145 (m, C≡C), 1254 (s), 1029 (s), 848 (s) cm^{-1}. **MS** (ESI^{+}-TOF): *m/z* 311 ($[M+Na]^{+}$, 28), 289 ($[M+H]^{+}$, 100). **HRMS** (EI^{+}): Cald. for $C_{13}H_{26}O_3PSi$ ($[M+H]^{+}$), 289.1386; found, 289.1383.

(1*E*,3*E*,5*E*,7*E*,9*E*)-1,10-Di(benzyldimethylsilyl)-3,8-dimethyldeca-1,3,5,7,9-pentaene (5).

Method A (Barbier conditions): *n*-BuLi (0.075 mL, 2.45 M in hexanes, 0.184 mmol) was added to a solution of HMDS (0.039 mL, 0.184 mmol) in THF (0.2 mL). After stirring at -78 °C for 30 min, this solution was added dropwise over a mixture of **15** (0.067 g, 0.184 mmol) and **14** (0.03 g, 0.123 mmol) in THF (0.25 mL) and the temperature was allowed to reach 25 °C over 21 h. Water was added and the resulting mixture was extracted with Et_2O (3x). The combined organic layers were washed with H_2O (3x) and brine (3x), and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 98:2 hexane/EtOAc) to afford 0.032 g (45%) of **5** as a colourless oil.

Method B: To a cooled (-78 °C) solution of **15** (0.112 g, 0.305 mmol) in THF (0.2 mL), *n*-BuLi (0.12 mL, 2.45 M in hexanes, 0.027 mmol) and HMDS (0.06 mL, 0.285 mmol) were added and the reaction was stirred for 30 min at -78 °C. A solution of **14** (0.05 g, 0.205 mmol) in THF (0.25 mL) was added, and the resulting solution was allowed to reach 25 °C and stirred for a total of 5 h. Water was added and the resulting mixture was extracted with Et_2O (3x). The combined organic layers were washed with H_2O (3x) and brine (3x), and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 98:2 hexane/EtOAc) to afford 0.023 g (25%) of **5** as a colourless oil.

Method C: To a cooled (0 °C) solution of **19** (0.39 g, 1.03 mmol) in MeOH (4.7 mL), K_2CO_3 (1.71 g, 12.36 mmol) was added. The mixture was stirred at 25 °C for 1 h and water was added. The resulting mixture was extracted with Et_2O (4x), the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. To a degassed solution of Pt(DVDS) (0.11 mL, 2% in xylene, 0.005 mmol) and P^tBu_3 (0.005 mL, 1M in toluene, 0.005 mmol) in THF (2.7 mL), $BnMe_2SiH$ (0.95 mL, 1.47 mmol) was added. After stirring for 30 min at 25 °C A solution of the residue obtained above (expected to be **21**) in THF (2.7 mL) was added and the reaction mixture was stirred at 25 °C for 2.5 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel, 98-2 hexane/EtOAc) to afford 0.25 g (56%) of **5** as a yellow oil. **^{1}H-NMR** (400.16 MHz, C_6D_6): δ 7.33 – 7.22 (m, 4H, ArH), 7.17 – 7.07 (m, 6H, ArH), 6.86 (d, *J* = 19.4 Hz, 2H, $2H_1$ or $2H_2$), 6.75 (d, *J* = 10.1 Hz, 2H, $2H_4$), 6.32 (d, *J* = 10.1 Hz, 2H, $2H_5$), 6.07 (d, *J* = 19.4 Hz, 2H, $2H_2$ or $2H_1$), 2.26 (s, 4H, 2xSi$Me_2$$\underline{CH_2}$Ph), 1.95 (s, 6H, 2x$C_3$-$CH_3$), 0.27 (s, 12H, 2xSi$\underline{Me_2}$Bn) pm. **^{13}C-NMR** (100.62 MHz, C_6D_6): δ 149.8 (d, 2x), 140.2 (s, 2x), 137.2 (s, 2x), 133.8 (d, 2x), 131.2 (d, 2x), 128.7 (d, 2x), 128.6 (d, 4x), 126.6 (d, 4x), 124.6 (d, 2x), 26.5 (t, 2x), 12.4 (q, 2x), -3.1 (q, 4x) ppm. **IR** (NaCl): υ 2954 (m, C-H), 2854 (m, C-H), 1568 (m), 1249 (m),

1151 (m), 772 (s) cm^{-1}. **MS** (ESI^+-TOF): *m/z* 458 (30), 457 ($[M+H]^+$, 100), 419 (72). **HRMS** (ESI^+): Calcd. for $C_{30}H_{41}Si_2$ ($[M+H]^+$), 457.2741; found, 457.2742.

(1*E*,3*E*,5*E*,7*E*)-Benzyl-[3,8-Dimethyl-10-(trimethylsilyl)deca-1,3,5,7-tetraen-9-yn-1-yl)]-dimethylsilane (19). To a cooled (-78 °C) solution of **17** (3.15 g, 10.93 mmol) in THF (91 mL), *n*-BuLi (4.7 mL, 2.3 M in hexanes, 10.93 mmol) and HMDS (2.3 mL, 10.93 mmol) were added. After stirring at -78 °C for 0.5 h, a solution of **14** (1.78 g, 7.28 mmol) in THF (70 mL) was added and the reaction mixture was allowed to warm slowly from -78 °C to 25 °C over 2 h. Water was added and the resulting mixture was extracted with Et_2O (3x). The combined organic layers were washed with H_2O (3x) and a saturated aqueous solution of NaCl (3x), and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, (¿SiO2 o C18-SiO2?) 98:2 hexane/EtOAc) to afford 1.3 g (77% yield) of **19** as a red oil. **^{1}H-NMR** (400.13 MHz, C_6D_6): δ 7.20 – 7.10 (m, 5H, $SiMe_2CH_2\underline{Ph}$), 7.09 – 6.96 (m, 3H), 6.51 – 6.32 (m, 2H), 6.04 (d, *J* = 11.0 Hz, 1H), 5.92 (d, *J* = 18.8 Hz, 1H), 2.11 (s, 2H, $SiMe_2\underline{CH_2}Ph$), 1.84 (s, 3H, C-CH_3), 1.70 (s, 3H, C-CH_3), 0.26 (s, 6H, $Si(\underline{CH_3})_3$), 0.11 (s, 6H, $Si\underline{Me_2}Bn$) ppm. **^{13}C-NMR** (100.16 MHz, C_6D_6): δ 149.6 (d), 140.1 (s), 138.2 (s), 137.8 (d), 133.3 (d), 131.4 (d), 129.9 (d), 128.6 (d, 2x), 128.5 (d, 2x), 127.1 (d), 124.6 (d), 119.3 (s), 110.2 (s), 95.4 (s), 30.4 (d), 26.4 (t), 17.6 (q), 12.4 (q), 0.2 (q, 2x), -3.1 (q, 3x) ppm. **IR** (NaCl): ν 2961 (m, C-H), 2847 (w, C-H), 2143 (w, C-C≡H), 1668 (s), 1250 (m), 844 (s) cm^{-1}. **UV** (MeOH): λ_{max} 239 nm. **MS** (ESI^+-TOF): *m/z* 379 ($[M+H]^+$, 100), 149 (23). **HRMS** (ESI^+): Calcd. for $C_{24}H_{35}Si_2$ ($[M+H]^+$), 379.2276; found, 379.2272.

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(1*E*,3*E*,5*E*,7*E*,9*E*)-[9-(Benzyldimethylsilyl)-3,8-dimethylocta-1,3,5,7,9-pentaen-1-yl]-dimethylsilanol (6). Mention method C? To a cooled (0 °C) solution of **19** (0.614 g, 1.621 mmol) in MeOH (7.4 mL), K_2CO_3 (2.688 g, 19.452 mmol) was added. The reaction mixture was stirred at 25 °C for 1 h and water was added. The mixture was extracted with Et_2O (4x), the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was used in the next step without further purification.

INCOMPLETE To a solution of Pt(DVDS) (0.157 mL, 2% in xylene, 0.007 mmol) and ^{t}Bu$_3$P (7 µL, 1 M in toluene, 0.007 mmol) in THF (5 mL), ethoxydimethylsilane (0.224 g, 2.153 mmol) was added and the mixture was stirred for 1 h at 25 °C. Then the solvent was evaporated. To a solution of the residue obtained above in CH_3CN (15 mL) an aqueous buffer solution HOAc/NaOAc (1.0 M, 15 mL, pH 5.0) was added and the resulting mixture was stirred at 25 °C for 15 h. Water was added and the aqueous layers were extracted with Et_2O (3x). The combined organic layers were washed with water (2x) and a saturated aqueous solution of NaCl (2x) and dried and the solvent was evaporated. The residue was purified by column chromatography (silica

gel, 85:15 hexane/EtOAc) to afford 0.237 g (43%) of **6** as a yellow oil. **^{1}H-NMR** (400.13 MHz, C_6D_6): δ 7.21 – 7.17 (m, 2H, ArH), 7.07 – 6.95 (m, 3H, ArH), 6.86 (d, *J* = 18.8 Hz, 1H), 6.73 (d, *J* = 18.8 Hz, 1H), 6.69-6.60 (m, 2H), 6.30-6.20 (m, 2H), 5.93 (d, *J* = 18.8 Hz, 1H), 5.92 (d, *J* = 18.8 Hz, 1H), 2.13 (s, 2H, $SiMe_2\underline{CH_2}Ph$), 1.82 (s, 6H, 2xC-CH_3), 0.23 (s, 6H, $Si(OH)\underline{Me_2}$ or $Si\underline{Me_2}Bn$), 0.13 (s, 6H, $Si(OH)\underline{Me_2}$ or $Si\underline{Me_2}Bn$) ppm. **^{13}C-NMR** (100.16 MHz, C_6D_6): δ 149.7 (d, 2x), 140.2 (s), 137.3 (s), 137.2 (s), 134.2 (d), 133.7 (d), 131.3 (d), 131.2 (d), 128.7 (d, 2x), 128.6 (d, 2x), 127.5 (d), 126.6 (d), 124.6 (d), 26.5 (t), 12.4 (q, 2x), 0.6 (q, 2x), -3.1 (q, 2x) ppm. **IR** (NaCl): ν 2956 (m, C-H), 1568 (w), 1214 (w), 843 (m), 771 (s) cm^{-1}. **UV** (MeOH): λ_{max} 372, 353 nm. **MS** (ESI^+-TOF): *m/z* 383 ($[M+H]^+$, 100), 362 (18), 341 (13), 301 (15), 270 (19), 242 (18). **HRMS** (EI^+): Calcd. for $C_{23}H_{35}OSi_2$ ($[M+H]^+$), 383.2218; found, 383.2210.

(1*E*,3*E*,5*E*,7*E*,9*E*)-Benzyl-10-(ethoxydimethylsilyl)-3,8-dimethyldeca-1,3,5,7,9-pentaen)dimethylsilane (21). To a cooled (0 °C) solution of **19** (0.65 g, 1.72 mmol) in MeOH (7.8 mL), K_2CO_3 (2.85 g, 20.60 mmol) was added. The mixture was stirred at 25 °C for 1 h and water was added. The resulting mixture was extracted with Et_2O (4x), the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated.

To a solution of Pt(DVDS) (0.18 mL, 2% in xylene, 0.008 mmol) and ^{t}Bu$_3$P (8 µL, 1 M in toluene, 0.008 mmol) in THF (5 mL), ethoxydimethylsilane (0.25 g, 2.45 mmol) was added and the mixture was stirred for 30 min at 25 °C. A solution of the residue obtained above (0.5 g, 1.63 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 1 h. The solvent was evaporated and the residue was purified by chromatography (C18 - silica gel, MeCN) to afford 0.45 g (68% yield) of a yellow oil identified as (1*E*,3*E*,5*E*,7*E*,9*E*)-benzyl-10-(ethoxydimethylsilyl)-3,8-dimethyldeca-1,3,5,7,9-tetraen-1-yl)dimethylsilane **21**. **^{1}H-NMR** (400.16 MHz, C_6D_6): δ 7.20 – 7.15 (m, 2H, ArH), 7.07 – 7.00 (m, 3H, ArH), 6.93 (d, *J* = 18.9 Hz, 1H), 6.73 (d, *J* = 18.8 Hz, 1H), 6.62 (dd, *J* = 7.7, 3.0 Hz, 2H), 6.21 (dd, *J* = 24.4, 8.5 Hz, 2H), 6.01 (d, *J* = 18.9 Hz, 1H), 5.95 (d, *J* = 18.8 Hz, 1H), 3.66 (q, *J* = 7.0 Hz, 2H, $SiMe_2O\underline{CH_2}CH_3$), 2.13 (s, 2H, $SiMe_2\underline{CH_2}Ph$), 1.81 (s, 6H, 2xCH_3), 1.19 (t, *J* = 7.0 Hz, 3H, $SiMe_2OCH_2\underline{CH_3}$), 0.31 (s, 6H, $Si\underline{Me_2}OEt$), 0.12 (s, 6H, $Si\underline{Me_2}Bn$) ppm. **^{13}C-NMR** (100.62 MHz, C_6D_6): δ 150.3 (d), 149.5 (d), 140.2 (d), 137.3 (s), 137.2 (s), 134.3 (s), 133.7 (d), 131.4 (d), 131.1 (d), 128.7 (d, 2x), 128.5 (d, 2x), 126.7 (d), 126.2 (d), 124.6 (d), 58.5 (t), 26.5 (t), 19.0 (q), 12.4 (q, 2x), -1.2 (q, 2x), -3.1 (q, 2x) ppm. **IR** (NaCl): υ 1644 (m), 1219 (m), 834 (s), 679 (s) cm^{-1}. **HRMS** (EI^+): Calcd. for $C_{25}H_{39}OSi_2$ ($[M+H]^+$), 411.2538; found, 411.2534.

(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*)-Benzyldimethyl-[3,8,12-trimethyl-14-(2,6,6-trimethylcyclohex-1-en-1-yl)-tetradeca-1,3,5,7,9,11,13-heptaen-1-yl)-silane (23). To a solution of **6** (24.1 mg, 0.063 mmol) in dioxane (0.126 mL) was added TMSOK (0.063 mL, 2M in THF, 0.126 mmol).

After stirring for 15 min at 25 °C, a solution of **1** (20 mg, 0.063 mmol) in dioxane (0.126 mL) and $Pd(dba)_2$ (1.2 mg, 0.002 mmol) were added and the reaction mixture was stirred at 25 °C for 1.5 h. Then, the reaction mixture was filtered through a silica gel plug silica gel (SiO2, C18-SiO2, CN-SiO2)?, the solids were washed with AcOEt (3x) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 98:2 hexane/EtOAc) to afford 18.4 mg (59%) of **24** as an orange oil. **^{1}H-NMR** (400.13 MHz, $(CD_3)_2CO$): δ 7.27 – 7.16 (m, 2H, ArH), 7.14 – 6.99 (m, 3H, ArH), 6.84 – 6.70 (m, 3H), 6.66 (d, *J* = 18.8 Hz, 1H), 6.41 (d, *J* = 15.0 Hz, 1H), 6.4 – 6.32 (d, *J* = 10.5 Hz, 2H), 6.26 – 6.17 (m, 3H), 5.91 (d, *J* = 18.8 Hz, 1H), 2.20 (s, 2H, $SiMe_2\underline{CH_2}Ph$), 2.04 (m, 2H, $2H_4$), 1.99 (s, 6H, 2xC-CH_3), 1.89 (s, 3H, C-CH_3), 1.71 (s, 3H, C-CH_3), 1.66 – 1.58 (m, 2H), 1.52 – 1.46 (m, 2H), 1.04 (s, 6H, C_1-$(CH_3)_2$), 0.08 (s, 6H, $Si\underline{Me_2}Bn$) ppm. **^{13}C-NMR** (100.16 MHz, $(CD_3)_2CO$): δ 150.3 (d), 141.1 (s), 139.0 (d), 138.9 (s), 138.4 (d), 137.9 (s), 137.5 (s), 136.9 (s), 134.6 (d), 133.4 (d, 2x), 132.2 (d), 131.0 (s), 129.9 (d, 2x), 129.3 (d, 2x), 129.1 (d), 127.5 (d), 127.0 (d), 126.5 (d), 125.0 (d), 40.6 (t), 35.1 (s), 33.8 (t), 26.7 (q), 22.1 (t), 20.1 (q), 13.0 (t), 12.5 (q), 12.5 (q), -2.9 (q, 2x) ppm. **IR** (NaCl): ν 2921 (s, C-H), 1566 (w), 960 (s), 847 (s) cm^{-1}. **UV** (MeOH): λ_{max} 403, 373, 352 nm. **MS** (ESI^+-TOF): *m/z* 497 ($[M+H]^+$, 2), 413 (8), 285 (18), 356 (13), 255 (100). **HRMS** (ESI^+): Calcd. for $C_{35}H_{49}Si$ ($[M+H]^+$), 497.3595; found, 497.3598.

β,β-Carotene (7).

Method A: Preparation of **7** from symmetrical bissilyl reagent **5**. To a cooled (0 °C) solution of **5** (12.2 mg, 0.027 mmol) in THF (0.76 mL) was added TBAF (0.061 mL, 1M in THF, 0.061 mmol). After stirring for 40 min at 0 °C, a solution of **1** (12.0 mg, 0.038 mmol) in THF (0.76 mL) and $Pd_2dba_3{\cdot}CHCl_3$ (5.9 mg, 0.006 mmol) were added and the reaction mixture was stirred at 0 °C for 1 h and at 25 °C for 15 min. After reaction completion (as indicated by tlc), a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4) and concentrated. After purification by column chromatography (CN-silica gel, 98:2 hexane/EtOAc), 20.4 mg (61%) of an orange oil identified as β,β-carotene **7** were isolated.{Vaz, 2002 #1629}

Method B: One-pot sequential preparation of **7** from bissilyl reagent **6** without isolation of monosilane **23**. To a solution of **6** (36.4 mg, 0.095 mmol) in dioxane (0.45 mL) was added TMSOK (0.095 mL, 2M in THF, 0.190 mmol). After stirring for 15 min at 25 °C, a solution of **1** (30 mg, 0.095 mmol) in dioxane (0.5 mL) and $Pd(dba)_2$ (1.2 mg, 0.002 mmol) were added and the reaction mixture was stirred at 25 °C for 1.5 h. Then, the reaction mixture was filtered through a silica gel plug, the solids were washed with AcOEt (3x), and the solvent was evaporated. The residue was dissolved in THF (0.5 mL) and TBAF (0.190 mL, 1M in THF, 0.190 mmol) was then added. After stirring for 15 min at 25 °C, a solution of **5** (30 mg, 0.095 mmol) in THF (0.5 mL) and $Pd(dba)_2$ (1.2 mg, 0.002 mmol) were added and the reaction mixture was stirred at 25 °C for

1.5 h. Then, the reaction mixture was filtered through a silica gel plug, the solids were washed with AcOEt (3x) and the solvent was evaporated. After purification by column chromatography (CN-silica gel, 98:2 hexane/EtOAc), 33.8 mg (66%) of an orange oil identified as β,β-carotene **7** were isolated.{Vaz, 2002 #1629}

*Method C: (Preparation of 7 from monosilane **23**)* TBAF (0.066 mL, 0.066 mmol, 1M in THF) was added to a cooled (0 °C) solution of **23** (33 mg, 0.066 mmol) in THF (0.6 mL). After stirring for 30 min at 0 °C, a solution of **1** (20 mg, 0.063 mmol) in THF (0.766 mL) and $Pd_2dba_3 \cdot CHCl_3$ (3.3 mg, 0.003 mmol) were added and the reaction mixture was stirred at 0 °C for 1 h and at 25 °C for 15 min. After completion, a saturated aqueous solution of NH_4Cl was added and the reaction mixture was extracted with Et_2O (3x). The combined organic layers were washed with a saturated aqueous solution of NaCl (1x), dried and concentrated. After purification by column chromatography (CN-silica gel, 98:2 hexane/EtOAc), 30.5 mg (90%) of an orange oil identified as β,β-carotene **7** were isolated.{Vaz, 2002 #1629}

(3*R*,3'*R*)-zeaxanthin (8). TBAF (0.072 mL, 1M in THF, 0.072 mmol) was added to a cooled (0 °C) solution of **5** (14.4 mg, 0.032 mmol) in THF (0.9 mL). After stirring for 40 min at 0 °C, a solution of **22**{Vaz, 2002 #1629} (15.0 mg, 0.045 mmol) in THF (0.9 mL) and $Pd_2dba_3 \cdot CHCl_3$ (7.1 mg, 0.007 mmol) were added and the reaction mixture was stirred at 0 °C for 1h and at 25 °C for 15 min. After completion, a saturated aqueous solution of NH_4Cl was added and the resulting mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried and concentrated. After purification by column chromatography (CN-silica gel, 90:10 hexane/EtOAc), 14 mg (55%) of an orange oil identified as (3*R*,3'*R*)-zeazanthin **8** were isolated.{Vaz, 2002 #1629}

9-*cis*-β,β-Carotene (9).

Method A: TBAF (0.205 mL, 1 M in THF, 0.205 mmol) was added to a cooled (0 °C) solution of **23** (45.2 mg, 0.091 mmol) in THF (1.6 mL). After stirring for 30 min, a solution of **24** (25 mg, 0.079 mmol) in THF (1.6 mL) and $Pd_2dba_3 \cdot CHCl_3$ (8.3 mg, 0.008 mmol) were added. After stirring at 25 °C for 2.5 h, a saturated aqueous solution of NH_4Cl was added. The mixture was extracted with EtOAc (3x) and the combined organic layers were washed with a saturated aqueous solution of NaCl (3x) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 90:7:3 hexane/EtOAc/Et_3N) to afford 25.4 mg (60%) of a red oil identified as 9-*cis*-β,β-carotene **9**.

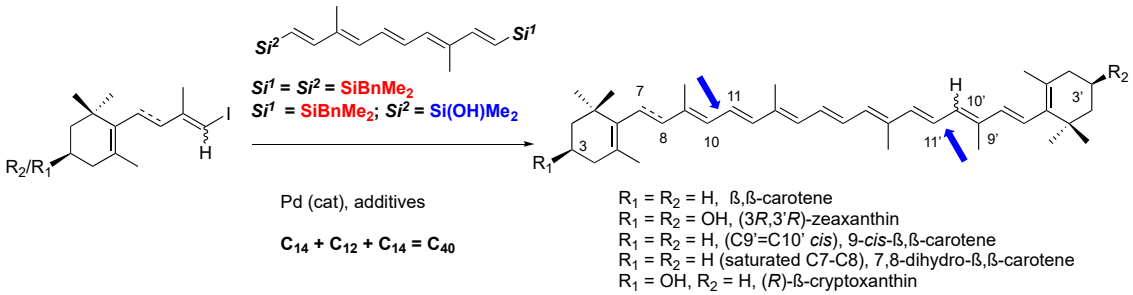
Method B (one pot): TMSOK (0.026 mL, 2M in THF, 0.052 mmol) was added to a solution of **6** (9.9 mg, 0.026 mmol) in dioxane (0.3 mL). After stirring for 15 min at 25 °C, (1*E*,3*E*)-4-iodo-3-methylbuta-1,3,3-trimethylcyclohex-1-ene **1** (8.3 mg, 0.026 mmol) in dioxane (0.3 mL) and $Pd(dba)_2$ (0.6 mg, 0.001 mmol) were added and the reaction mixture was stirred at

25°C for 1.5 h. Then, the reaction mixture was filtered through a silica gel plug, washing with AcOEt (3x) and the solvent was evaporated. TBAF (0.052 mL, 1M in THF, 0.052 mmol) was then added to the solution of the residue in THF (0.5 mL). After stirring for 15 min at 25 °C, a solution of **24** (8.2 mg, 0.026 mmol) in THF (0.5 mL) and $Pd(dba)_2$ (0.6 mg, 0.001 mmol) were added and the reaction mixture was stirred at 25 °C for 1.5 h. Then, the reaction mixture was filtered through a silica gel plug, washing with AcOEt (3x) and the solvent was evaporated. After purification by column chromatography (CN-silica gel, 98:2 hexane/EtOAc), 4.5 mg (32%) of an orange oil identified as 9-*cis*-β,β-carotene **9** were isolated. **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 6.74 (dd, *J* = 14.8, 11.6 Hz, 2H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.66 – 6.54 (m, 3H), 6.28 (d, *J* = 14.9 Hz, 1H), 6.26 – 6.19 (m, 2H), 6.19 – 6.08 (m, 4H), 6.05 (d, *J* = 11.5 Hz, 1H), 2.08 – 1.99 (m, 4H), 1.97 (s, 6H), 1.95 (s, 6H), 1.76 (s, 3H), 1.71 (s, 3H), 1.66 – 1.59 (m, 4H), 1.51 – 1.39 (m, 4H), 1.04 (s, 6H), 1.03 (s, 6H) ppm. **^{13}C-NMR** (100.16 MHz, $CDCl_3$): δ 138.4 (s), 138.1 (s), 137.8 (d), 136.7 (d), 136.4 (s, 2x), 136.1 (s), 134.6 (d), 130.9 (d), 132.4 (d), 130.2 (d, 3x), 130.0 (d), 129.6 (s, 2x), 129.5 (d, 2x), 128.5 (d), 127.1 (s), 127.0 (d), 123.8 (d), 39.7 (t, 2x), 34.4 (s, 2x), 33.3 (t, 2x), 29.1 (q), 28.6 (q, 2x), 22.0 (q), 21.9 (q), 20.9 (q), 19.4 (t, 2x), 13.0 (q), 12.9 (q) ppm. **UV** (MeOH): λ_{max} 426 nm. **HRMS** (ESI^+): Calcd. for $C_{40}H_{56}$ ($[M+H]^+$), 536.4375; found, 536.4376.

7,8-Dihydro-β,β-carotene (10).{Takaichi, 1996 #1804} TBAF (0.33 mL, 0.33 mmol, 1M in THF) was added to a cooled (0 °C) solution of **23** (72 mg, 0.145 mmol) in THF (1.3 mL). After stirring for 30 min at 0 °C, a solution of **25** (40 mg, 0.126 mmol) in THF (1.3 mL) and $Pd_2dba_3{\cdot}CHCl_3$ (13 mg, 0.013 mmol) were added and the reaction mixture was stirred at 0 °C for 1h and. at 25 °C for 15 min. After completion, a saturated aqueous solution of NH_4Cl was added and the resulting mixture was extracted with Et_2O (3x). The combined organic layers were washed with a saturated aqueous solution of NaCl (1x), dried and concentrated under *vacuum*. After purification by column chromatography (CN-silica gel, 98:2 hexane/EtOAc), 53 mg (78%) of an orange solid identified as 7,8-dihydro-β,β-carotene **10** were isolated. **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 6.50 – 6.09 (m, 11H), 5.98 (d, *J* = 11.1 Hz, 1H), 2.02 (t, *J* = 6.0 Hz, 4H, 2xCH_2), 1.97 (s, 6H, C-CH_3 + C-CH_3), 1.95 (s, 3H, C-CH_3), 1.94 – 1.89 (m, 4H, 2xCH_2), 1.87 (s, 3H, C-CH_3), 1.72 (s, 3H, C-CH_3), 1.63 (s, 3H, C-CH_3), 1.62 – 1.54 (m, 4H, 2xCH_2), 1.49 – 1.45 (m, 4H, 2xCH_2), 1.45 – 1.41 (m, 4H, 2xCH_2), 1.03 (s, 6H, C-$(CH_3)_2$), 1.01 (s, 6H, C-$(CH_3)_2$) ppm.{Takaichi, 1996 #1804} **^{13}C-NMR** (100.16 MHz, $CDCl_3$): δ 140.8 (s), 138.1 (s), 138.0 (d), 137.4 (d), 136.6 (d), 136.3 (s), 136.0 (d), 135.5 (s), 135.4 (d), 132.6 (d), 131.6 (d), 131.0 (d), 130.2 (d), 129.6 (d), 129.5 (s), 127.4 (s), 126.7 (s), 125.3 (d), 125.2 (s), 125.0 (d), 41.0 (t), 40.0 (t), 39.8 (t), 35.2 (s), 34.4 (s), 33.3 (t), 32.9 (t), 29.1 (q, 2x), 28.8 (q, 3x), 27.9 (t), 21.9 (q), 20.0 (q), 19.7 (t), 19.4 (t), 17.2 (q), 13.0 (q, 2x) ppm. **IR** (NaCl): ν 2927 (s, C-H), 2364 (w, C-H), 1447 (w), 965 (s) cm^{-1}. **HRMS** (ESI^+): Calcd. for $C_{40}H_{58}$ ($[M+H]^+$), 538.4525; found, 538.4533.

(3*R*)-β-Cryptoxanthin (11). TMSOK (0.057 mL, 2M in THF, 0.114 mmol) was added to a solution of **6** (22 mg, 0.057 mmol) in dioxane (0.5 mL). After stirring for 15 min at 25 °C, a solution of **1** (18 mg, 0.057 mmol) in dioxane (0.5 mL) and $Pd(dba)_2$ (1 mg, 0.001 mmol) were added and the reaction mixture was stirred at 25°C for 1.5 h. Then, the reaction mixture was filtered through a silica gel plug, washing with AcOEt (3x) and the solvent was evaporated. TBAF (0.114 mL, 1M in THF, 0.114 mmol) was added to the solution of the residue in THF (0.5 mL). After stirring for 15 min at 25 °C a solution of **22**{Vaz, 2002 #1629} (22 mg, 0.057 mmol) in THF (0.5 mL) and $Pd(dba)_2$ (1 mg, 0.001 mmol) were added and the reaction mixture was stirred at 25 °C for 1.5 h. Then, the reaction mixture was filtered through a silica gel plug, washing with AcOEt (3x) and the solvent was evaporated. After purification by column chromatography (CN-silica gel, 90:10 hexane/EtOAc), 18 mg (57%) of an orange oil identified as (3*R*)-β-cryptoxanthin **11** were isolated.{Khachik, 2007 #2609} <DATOS?

GRAPHICAL ABSTRACT



$R_1 = R_2 = H$, ß,ß-carotene
$R_1 = R_2 = OH$, (3*R*,3'*R*)-zeaxanthin
$R_1 = R_2 = H$, (C9'=C10' *cis*), 9-*cis*-ß,ß-carotene
$R_1 = R_2 = H$ (saturated C7-C8), 7,8-dihydro-ß,ß-carotene
$R_1 = OH$, $R_2 = H$, (*R*)-ß-cryptoxanthin