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Total Synthesis of Enantiopure Pyrrhoxanthin: Alternative Methods for the Stereoselective Preparation of 4-Alkylidenebutenolides

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Abstract: A new stereocontrolled total synthesis of the configurationally labile C_{37}-norcarotenoid pyrrhoxanthin in enantiopure form has been completed. A highly stereoselective Horner–Wadsworth–Emmons (HWE) condensation of a C_{17}-allylphosphonate and a C_{20}-aldehyde was used as the last conjunctive step. Both a Sonogashira reaction to form the C_{17}-phosphonate and the final HWE condensation proved to be compatible with the sensitive C7–C10 enyne *E* configuration. Regioselective (5-*exo*-dig) silver-promoted lactonization reactions of three alternative pent-2-en-4-ynoic acid precursors with increased complexity, including a fully functionalized C_{20}-fragment, were explored for the preparation of the γ-alkylidenebutenolide fragment. This survey extends the existing methodologies for the preparation of oxygen-containing carotenoids (xanthophylls) and streamlines the synthesis of additional members of the C_{37}-norcarotenoid butenolide family of natural products.

Keywords: catalysis · marine carotenoids · polyenes · pyrrhoxanthin · total synthesis

Introduction

Algae are responsible for about 50% of the photosynthesis that takes place on Earth. Therefore, these organisms play an important role in leveling the continuously increasing excess of carbon dioxide in the atmosphere. Carotenoids play an important dual role in photosynthetic organisms because they act as antennae that transfer the Sun's energy to chlorophylls and hence to the photoreaction centers, and also protect the natural photosystems from damage caused by excess light.[1,2] Among the wide variety of carotenoids isolated from marine organisms, the xanthophylls (oxygen-containing carotenoids) peridinin and fucoxanthin are the most abundant. The exceptional electronic properties of these pigments have been selected by evolution to serve for optimal light-harvesting and photoprotection of the pigment-protein complexes in the marine environments.[1]

The structure of the acetylenic C_{37}-norcarotenoid pyrrhoxanthin **1**[3,4] (Figure 1) is closely related to that of peridinin, since both share a shortened polyene chain with an atypical arrangement of methyl groups in comparison to parent C_{40} carotenoids.[5,6] Isolated from microalgae and planktonic dinoflagellates,[3,4] the structure of **1** was elucidated by Liaaen-Jensen and co-workers in 1980.[7] It features an all-*trans* polyene chain with an inserted butenolide unit spanning C9–C11 and a C7′≡C8′ triple bond, that connect 5,6-epoxy-3-hydroxycyclohexane and 3-acetoxycyclohexene termini containing the stereogenic centers.

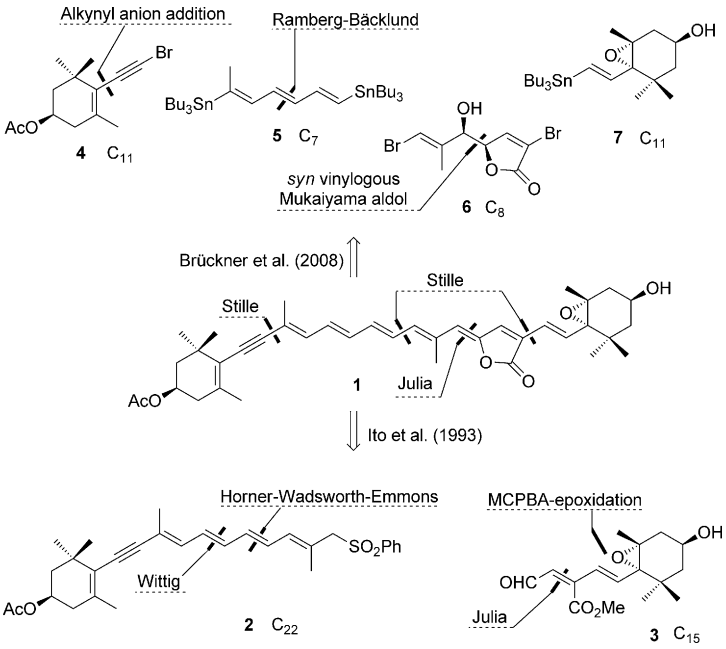

Figure 1. Previous reported total syntheses of pyrrhoxanthin based on double- (bottom)[8] and single-bond (top)[10] disconnection strategies. MCPBA = *meta*-chloroperbenzoic acid.

The first total synthesis[8] of peridinin and pyrrhoxanthin became a milestone in the carotenoid field given the challenges posed by their structures. In particular, the butenolide ring present in both xanthophylls was assembled concomitantly with a double bond formation using the conjunctive Julia-type condensation of allylic sulfone **2** and alde-

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hyde **3**. The alkoxysulfone intermediate underwent acyl substitution of the β-methoxycarbonyl group, and elimination of sulfinic acid to furnish the alkylidenebutenolide and provide the C_{37}-norcarotenoid skeleton (Figure 1). However, the low yield and poor stereocontrol of this step, as well as others that formed double bonds to access the highly functionalized C_{22} unit **2**, and the oxirane ring in the C_{15}-fragment **3** reduced the efficiency of the synthetic route. Moreover, the unusual instability of the *E* enyne fragments in intermediates and the final pyrrhoxanthin skeleton was noted, as isomerization to the *Z* isomers easily occurred.[9]

The first total synthesis of enantiopure pyrrhoxanthin[10] was based on the assembly of four fragments of similar complexity (**4**–**7**, Figure 1) within a $C_{11}+C_7+C_8+C_{11}$ synthetic scheme. The functionalization of the building blocks enabled the application of three Stille cross-coupling reactions, the last two in sequence, to assemble the xanthophyll skeleton and form the configurationally unstable *E* enyne. This new synthetic route illustrates the unmatched potential of the metal-catalyzed cross-coupling processes as efficient tools for the synthesis of complex polyenes. These processes take place preferentially with retention of configuration of the coupling partners, and in the case of difunctionalized substrates positional selectivity can be achieved, which allows the use of iterative cross-coupling sequences in the synthetic scheme.[11–13] In the case of pyrrhoxanthin, the non-symmetrical C_8-dibromide and the C_7-bis-metallated linchpins, **6** and **5**, reacted preferentially at the most electron-deficient and at the least-hindered positions, respectively.

We have reported an alternative stereocontrolled approach to pyrrhoxanthin[14] that is also based on the generation of single bonds connecting Csp^2 atoms through metal-catalyzed cross-coupling reactions (Figure 2). Following this strategy, the consecutive Stille cross-coupling reactions of a central C_8-dihalogenated alkylidenebutenolide **9** with the appropriate C_{18}- and C_{11}-alkenylstannanes (**8** and **10**, respectively) completed the construction of the carbon skeleton of the acetylenic C_{37}-norcarotenoid. Due to the different reactivity of bromides and iodides, a halogen-selective Stille reaction was possible in **9**. All the stereochemical elements present in each of the fragments required for the total synthesis of the C_{37}-norcarotenoid skeleton were prepared with complete stereocontrol. The C_{18}-tetraenyne with *Z* geometry was obtained by Julia–Kocienski condensation[15,16] of unsaturated BT sulphone **12** and unsaturated aldehyde **11**,[17,18] but the polyene was expected to isomerize to the all-*trans* isomer upon subsequent Pd-catalyzed coupling. However, the C9′–C12′ *E*,*Z*-enyne moiety present in this complex structure underwent double-isomerization to the corresponding *Z*,*E* geometry during the Stille coupling and, as a consequence, the product obtained was the 9′*Z* isomer of the natural carotenoid, (9′*Z*)-**1**.[14]

To overcome this limitation of the Julia–Stille–Stille route to acetylenic carotenoids,[14] we devised a new stereoselective approach to pyrrhoxanthin **1** that excluded palladium complexes in the step(s) following enyne formation. Instead, a highly stereocontrolled connective reaction for formation of the *E* C15=C15′ double bond was sought. The preservation of the sensitive natural *E* geometry of the enyne at C9′=C10′ limits the choice of the chemistry that is suitable for this step. The previously used (Sylvestre) Julia olefination between unsaturated benzothiazolyl sulfones and aldehydes was ruled out due to the undesired stereochemical outcome observed in the course of polyene synthesis.[17–19] Alternatives based on Wittig-type reactions were also explored.[20] Wittig reactions of aldehydes with the anions of functionalized triphenyl-[20] and more recently tributylphosphonium halides,[21,22] have been used for the stereoselective synthesis of different carotenoids. Concerns about the reactivity of the oxirane present at one of the end-groups during both the preparation of the phosphonium salt (acidic conditions) and the ylide formation steps (strong basic conditions),[23] as both acids and bases could induce the ring expansion of the original 5,6-alkenyloxirane into the corresponding 5,8-dihydrofuran ring,[24,25] excluded the functionalization of this fragment with the anion-stabilizing group. A recently reported olefination between semi-stabilized triphenylphosphonium ylides and appropriate imines[26] took place in our hands with random geometrical outcome. This led us to use the Horner–Wadsworth–Emmons (HWE) condensations for the synthesis of **1** by using functionalized C_{17}-allylphosphonate **15** and C_{20}-aldehyde **18**. For the success of the synthetic plan, the Sonogashira reaction[27] between the known terminal enyne **16**[14] and dienyliodide **17** to connect positions C8′ and C9′ should take place with preservation of the original double-bond geometry of **17** (Figure 3). For the C_{20}-aldehyde **18**, the stereocontrolled formation of the central γ-alkylidenebutenolide[28] unit was more challenging, but some alternatives to this structure have been reported.[29–33] Nevertheless, we decided to explore other routes to butenolides, which are discussed in the next section.

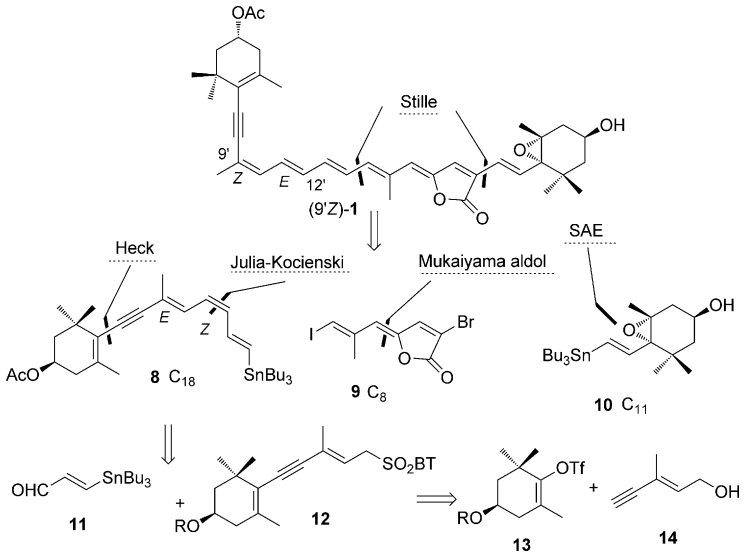

Figure 2. Previous total synthesis of (9′*Z*)-pyrrhoxanthin (9′*Z*-**1**) by using a Julia–Stille–Stille reaction sequence.[14]

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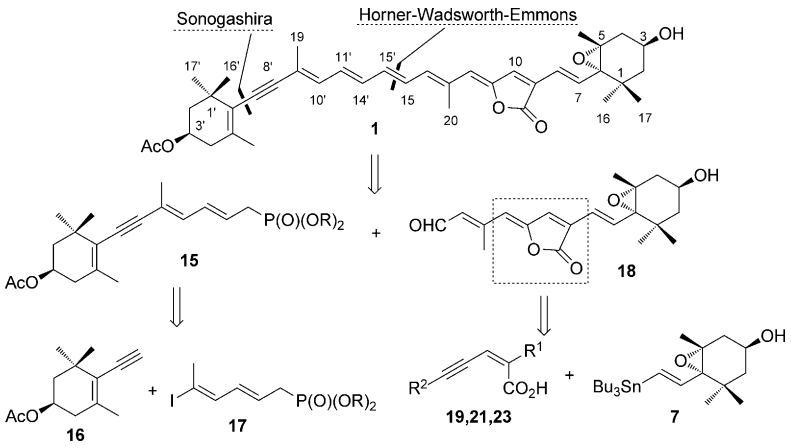

Figure 3. Proposed strategy for the stereocontrolled synthesis of pyrrhoxanthin (**1**).

Results and Discussion

The synthesis of the central γ-alkylidenebutenolide[28] linchpin to obtain the carotenoid butenolides shown in Figures 1 and 2 followed different strategies.[29–33] For example, the C_8-fragment **9** (Figure 2) was generated by the *syn*-selective vinylogous (extended) Mukaiyama aldol reaction of 3-bromo-2-trimethylsilyloxyfuran and (*E*)-3-iodo-2-methacrolein[32,33] followed by β-dehydration with PPh_3/diethyl azodicarboxylate (DEAD) in the dark. Fragment **6** (Figure 1) used in pyrrhoxanthin synthesis was obtained from tartrate by using as final steps the Ando's modification of the HWE reaction and lactone formation.[34] We envisioned the construction of the central butenolide fragment of **18** by the silver-promoted lactonization of pent-2-en-4-ynoic acids.[35] The regioselectivity of the cyclization is known to depend upon subtle electronic effects, but can be controlled by the choice of reagents: a Lewis acid, such as $ZnBr_2$, favors pyranone formation through 6-*endo*-dig addition to the polarized double bond, whereas an alkynophilic transition metal (Ag_2CO_3) affords regioisomeric furanone by 5-*exo*-dig cyclization (Figure 4). To further expand the use of butyrolactones in synthesis, three alternative substrates with increasingly complex pent-2-en-4-ynoic acid functionalities were explored. Substrates **19**, **21**, and **23** would in turn be made by following stereocontrolled synthetic routes by starting from doubly functionalized molecules **20**, **22**, and **24**, respectively, the last two incorporating a silane substituent as a halogen surrogate (Figure 4).

In the first approach, the butenolide core was constructed from the dienyne substrate **19** obtained by a selective Pd-catalyzed Sonogashira reaction of C_3-dibromoacrylate **20** with a suitable alkyne, as described in our recent work on the total synthesis of the C_{37}-norcarotenoid all-*trans*-(8*R*,6′*R*)-peridinin-5,8-furanoxide.[36] The second halide in the molecule allows the incorporation of additional fragments through Pd-catalyzed cross-coupling reactions. In the second approach, the enyne precursor of appropriate geometry **21** would be obtained by the *cis*-selective Still–Gennari olefination[37] between bis(trifluoroethyl)bromomethylphosphonate and protected propargylic aldehyde **22**. Likewise, the bromide would enable further functionalization of the carotenoid terminal group by a Stille reaction. In the third strategy, the fully-functionalized trienyne **23** would be acquired from the geometrically defined β-trimethylsilyl α-boron acrylate **24** by a consecutive Suzuki cross-coupling reaction, silane–iodine exchange, and Sonogashira reactions. The synthesis of this stereodefined bis-metallated reagent makes use of the catalyzed chemo- and stereoselective 1,2-addition of CuH to acetylenic esters and subsequent in situ copper-to-boron transmetalation with pinacolborane.[38]

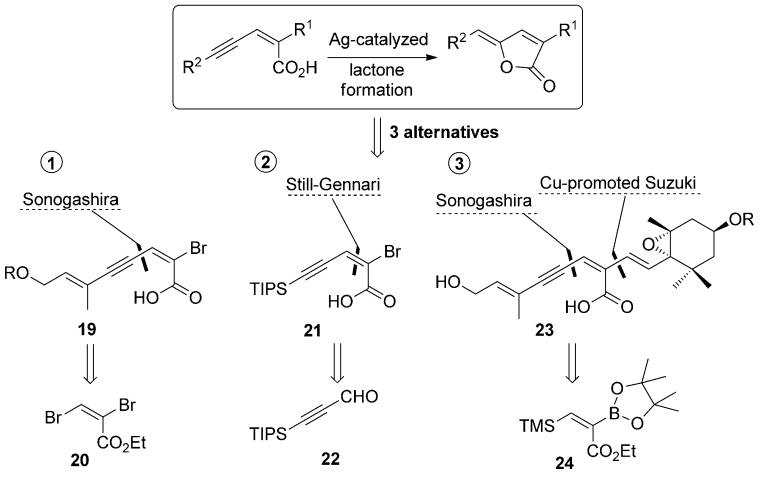

Figure 4. Synthetic routes to the central γ-alkylidenebutenolide.

The dienyne **19** required for the synthesis of the butenolide was prepared by the regioselective Sonogashira cross-coupling reaction of enyne **25** and ethyl (*E*)-2,3-dibromoacrylate **20** obtained upon treatment of methyl propiolate with $C_5H_5NH^+Br_3^-$ in CH_2Cl_2[39] (Scheme 1). Subsequent hydrolysis of the geometrically labile ester **26** under basic conditions and immediate silver-promoted cyclization of **19** provided the brominated γ-alkylidenebutenolide intermediate **27**. Upon Stille reaction with the readily available vinyl stannane **7**[14,32,40] under the conditions developed

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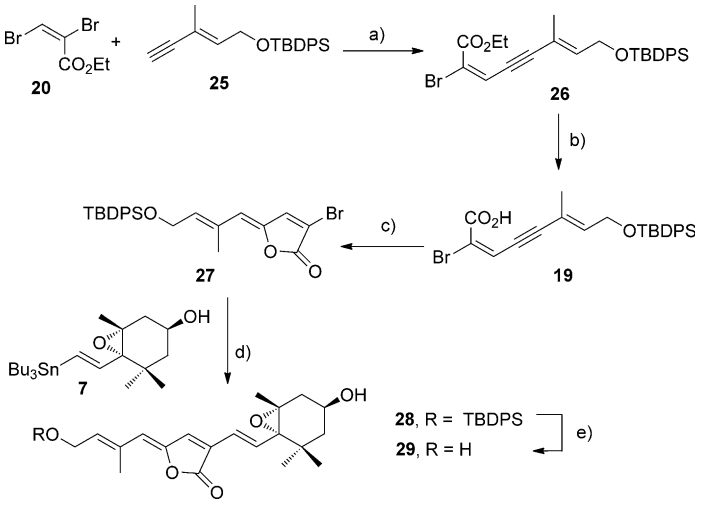
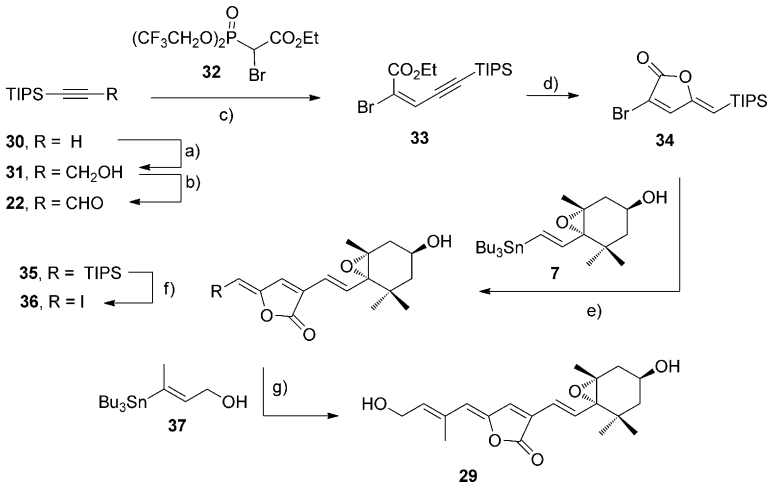


Scheme 1. a) $[PdCl_2(PPh_3)_2]$, CuI, 4:1 THF/Et_3N, 25 °C, 4 h, 87 %; b) LiOH·H_2O, THF/H_2O, 25 °C, 6 h; c) Ag_2CO_3, THF, 25 °C, 6 h (75 %, two steps); d) $[Pd(PPh_3)_4]$, CuTC, $[NBu_4][Ph_2PO_2]$, DMF, 0 °C, 3 h, 91 %; e) TAS-F, CH_3CN, 0 °C, 6 h, 37 %.

by Fürstner et al. for highly sensitive coupling partners,[41] namely $[Pd(PPh_3)_4]$ and copper(I)-thiophene-2-carboxylate (CuTC) catalysis in the presence of Liebeskind's phosphinite $[NBu_4][Ph_2PO_2]$, the expected product **28** was obtained exclusively as the all-*trans* isomer. The final deprotection of the primary alcohol turned problematic, due to the incompatibility of the labile oxirane ring with the typical tetrabutylammonium fluoride (TBAF)-based deprotection conditions, as traces of tetrabutylammonium hydroxide are present in the commercial reagent. As an alternative, the use of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F) (an easy to dry hypervalent silicon reagent and source of highly nucleophilic fluoride ions suitable for the deprotection of base- or acid-sensitive silyl ethers)[42] provided the expected allyl alcohol **29** and prevented the rearrangement of the 5,6-oxirane into the corresponding 5,8-furanoxide.[24,25]

The second approach based on the Still–Gennari[37] variant of the HWE olefination required the preparation of the silyl-protected propargylic aldehyde **22** prior to its reaction with bis(trifluoroethyl)bromomethylphosphonate **31** (Scheme 2). Conversion of triisopropylsilyl (TIPS)-protected acetylene **30** to the propargylic aldehyde **22** involved treatment with *n*BuLi and trapping the organolithium species with paraformaldehyde and subsequent oxidation of the alcohol **31** with pyridinium chlorochromate (PCC)/silicagel. Still–Gennari reaction of **22** with **32** in the presence of [18]crown-6 for the effective trapping of K^+ provided the brominated enyne **33** with excellent selectivity in good yield (86 %). Saponification of **33** afforded carboxylic acid **21** (Figure 4). The lactonization to the γ-alkylidenebutenolide **34** catalyzed by silver nitrate required heating **21** to 40 °C for 23 h. For the final Stille coupling between bromolactone **34** and vinylstannane **7**, the optimized conditions previously described[14,32,40] for the synthesis of peridinin and related carotenoids ($[Pd_2(dba)_3]$·$CHCl_3$, $(NBu_4)(Ph_2PO_2)$, 1:1 THF/DMF, 60 °C; dba = dibenzylideneacetone), afforded coupling product **35** in an acceptable yield only after extended reaction times (14 h), which could be substantially shortened (to 1 h) using the rate acceleration provided by copper salts and the phosphinite tin scavenger integrated in Fürstner's protocol.[41]

The proposed iododesilylation of **35** prior to the final Stille reaction faced problems likely due to the presence of the unprotected hydroxyl group, which competes with the silane in reactions with electrophilic halogenation agents. Most standard reaction conditions were unsuccessful: ICl in CH_2Cl_2 at 0 °C provided only degradation products, *N*-Iodosuccinimide (NIS) in CH_3CN returned **35**, NIS in $ClCH_2CN$ yielded a complex mixture of products, whereas I_2 in CH_2Cl_2 and IPy_2BF_4 in CH_3CN also failed to induce the exchange. Recently, Zakarian et al.[43] have demonstrated the beneficial effect of hexafluoroisopropanol (HFIP) on accelerating the rate of stereoselective iododesilylations of a variety of vinylsilanes. This solvent has also found utility in the cleavage of alkene-TIPS bonds assisted by Ag_2CO_3.[44] Thus, treatment of vinylsilane **35** with NIS, 2,6-lutidine, and Ag_2CO_3 in HFIP at room temperature gave rise to the iodide **36** with retention of the double-bond configuration. Final Stille coupling of **36** with vinyl stannane **37**[14,32,40] proceeded smoothly to afford the expected C_{20}-fragment **29** in good yield (90 %).



Scheme 2. a) *n*BuLi, HCHO, THF, −78 to 25 °C, 15 h, 95 %; b) PCC/Silica gel, CH_2Cl_2, 25 °C, 6 h, 92 %; c) KHMDS, [18]crown-6, THF, −78 °C, 1.5 h, 86 %; d) i) LiOH·H_2O, THF, 25 °C, 6 h; ii) $AgNO_3$, MeOH, 40 °C, 41 h, 68 % (2 steps); e) $[Pd(PPh_3)_4]$, CuTC, $[NBu_4][Ph_2PO_2]$, DMF, 25 °C, 1.5 h, 51 %; f) NIS, 2,6-lutidine, Ag_2CO_3, HFIP, −7 °C, 25 h, 88 %; g) $[Pd(PPh_3)_4]$, CuTC, $[NBu_4][Ph_2PO_2]$, DMF, 25 °C, 1 h, 90 %.

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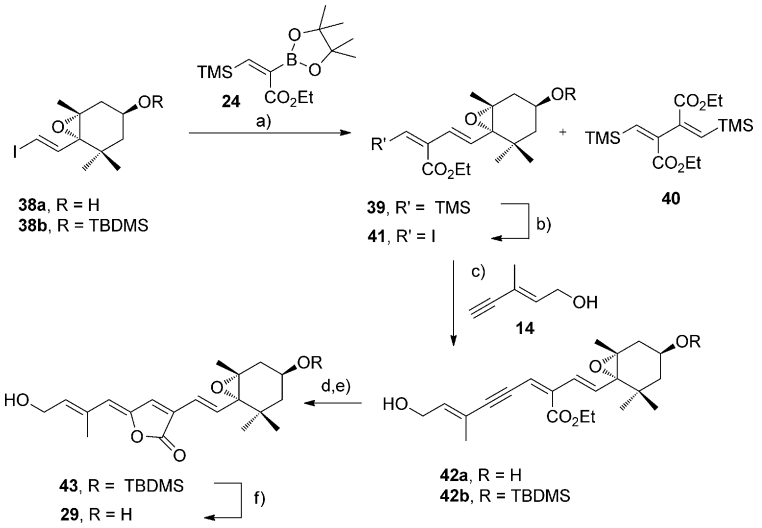

Scheme 3. a) $Pd(OAc)_2$, dppf, CuI, Cs_2CO_3, DMF, 0 to 25 °C, **39a**, 64 %; **39b**, 60 %; b) NIS, 2,6-lutidine, $(CF_3)_2CHOH$; **41a**, 89 %; **41b**, 81 %; c) $[Pd(PPh_3)_4]$, CuI, iPr_2NH, 25 °C, 1.8 h, **42a**, 82 %; **42b**, 77 %; d) KOH, MeOH, 70 °C, 30 min, 87 %; e) $AgNO_3$, MeOH, 25 °C, 1 h, 100 %; f) HCOOH, THF, H_2O, 0 °C, 74 %.

The third synthetic approach to the γ-alkylidenebutenolide core relies on Lipshutz's methodology for the stereoselective preparation of *Z*-configured β-TMS-substituted acrylates bearing a boronate group at the α-position (Scheme 3).[38] Applying this protocol, *Z*-pinacol boronate **24** was obtained as a single isomer from TMS-protected ethyl propiolate in fairly good yield. The boronate was then subjected to Suzuki coupling with alkenyliodide **38a**,[14,32,40] by using thallium hydroxide-accelerated conditions ($[Pd(PPh_3)_4]$, 10 % TlOH, THF, 25 °C). However, we experienced problems of reproducibility, and recovered unreacted starting vinyliodide in most cases. The lack of reactivity of the boronate, probably due to the electron-withdrawing effect of the geminal ester moiety, prompted us to use the copper-promoted Suzuki variant[45] recommended for electron-deficient boronates. The rate acceleration is likely a consequence of the transmetalation of boron to copper, which prevents the competing protodeboronation. By using $Pd(OAc)_2$, with 1,1′-bis(diphenylphosphino)ferrocene (dppf) as the ligand, CuI as additive, and Cs_2CO_3 in DMF, the desired product **39a** was isolated in good yield (64 %) together with small amounts of dimer **40**. The iododesilylation of the vinylsilane with a free hydroxyl group at C3 proceeded smoothly under Zakarian conditions and gave **41a**.[43] Sonogashira reaction[27] of **41a** with unprotected (*E*)-enynol **14** furnished **42a** in good yield (70 %), accompanied by small quantities of the alkyne homodimer. The hydrolysis of the ester in substrate **41a** with an unprotected hydroxyl group at C3 faced unanticipated problems. Treatment with aqueous LiOH in THF led to either no reaction at 25 °C or to degradation at higher temperatures (80 °C), probably due to side reactions involving the secondary alcohol. Alternative conditions were explored (2 M KOH, MeOH, 80 °C, 1.5 h (degradation); $KOSiMe_3$, THF, 45 °C, 3.5 h (degradation);[46] Me_3SnOH, 1,2-dichloroethane, 80 °C, 4 h (no reaction);[47] $Ba(OH)_2$, MeOH, 25 °C (partial degradation);[48] 2 M Na_2CO_3, MeOH, 70 °C, 3.5 h (degradation)), but unfortunately either complete or partial degradation of the starting ester occurred during the reaction.

Due to this shortcoming, the incorporation of a silyl ether protecting group was performed earlier in the synthesis. Thus, copper-accelerated Suzuki reaction[45] of **24** with the *tert*-butyldimethylsilyl (TBDMS)-protected vinyl iodide **38b** provided coupling product **39b** in good yield. Upon iododesilylation, the obtained vinyl iodide **41b** was successfully coupled to enynol **14** by treatment with $[Pd(PPh_3)_4]$ and CuI in a carefully degassed solution in iPr_2NH. Saponification of **42b** was successful in this case by using KOH in MeOH at 70 °C for 30 min, and the configurationally labile carboxylic acid **23** (Figure 4) was immediately subjected to lactonization promoted by $AgNO_3$ in MeOH, affording the fully functionalized γ-alkylidenebutenolide **43**. This oxacyclization is reminiscent of the Pd-promoted butenolide formation developed by Katsumura in the synthesis of peridinin.[19] Taking into account the presence of the sensitive oxirane in **43**, silyl ether deprotection was first attempted by using TAS-F as source of fluoride anion, but slow degradation of the starting product was observed. Successful deprotection to **29** (74 % yield) was achieved upon treating the silyl ether **43** with a solution of formic acid in THF/H_2O at 0 °C for 6 h.[49]

The synthesis of the C_{17}-phosphonate counterpart for the final HWE reaction started with the preparation of alkenyliodide **45**. Stereoretentive Sn/I exchange of the known[36] C_6-stannane **44** was induced by NIS in CH_3CN at 0 °C. The classical method for the transformation of the allylic alcohol into the corresponding phosphonate through the labile chloride intermediate followed by Arbuzov reaction with neat trimethyl phosphite and NaI provided the expected product **17b** although in low yield. Alternatively, the direct transformation induced by treatment of the alcohol with ZnI_2 and triethyl phosphite[50] gave rise to phosphonate **17a** in good yield. The Sonogashira reaction with enyne **16** by using $[Pd(PPh_3)_4]$ as the catalyst in the presence of CuI and Et_3N afforded the coupled product **15** (56 %). The stereostructure of **15** was established through analysis of NOE correlations (Scheme 4), which confirmed the 9′*E* configuration and the *trans* geometry of the remaining double bond.

To complete the norcarotenoid skeleton of **1**, alcohol **29** was first oxidized to **18** (95 % yield) with MnO_2 in slightly basic media (Na_2CO_3) to prevent undesired *E*/*Z* isomerization. The all-*trans* geometry of **18** was secured by ^1H NMR

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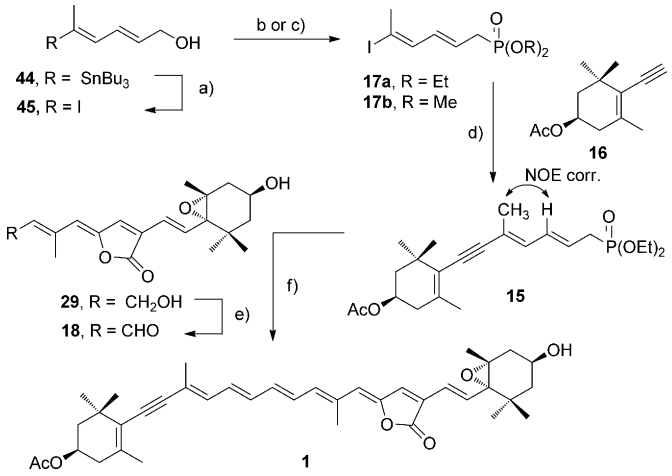

Scheme 4. a) NIS, CH_3CN, 0 °C, 1 h, 94 %; b) ZnI_2, $P(OEt)_3$, THF, 85 °C, 15 h, 70 %; c) i) MsCl, DMAP, CH_2Cl_2, 25 °C, 17 h; ii) $P(OMe)_3$, NaI, 70 °C, 6 h, 42 % (2 steps); d) $[Pd(PPh_3)_4]$, CuI, Et_3N, THF, 25 °C, 24 h, 56 %; e) MnO_2, Na_2CO_3, CH_2Cl_2, 0 °C, 20 min, 95 %; f) NaHMDS, THF, −78 °C, 15 min, 30 % (additional 10 % from the isolated β-hydroxyphosphonates).

spectroscopic analysis of coupling constants and NOESY-1d enhancements. The critical HWE reaction involved the in situ formation of the phosphonate-stabilized anion derived from **15** (sodium hexamethyl disilazide (NaHMDS), THF, −78 °C, 10 min) and addition of aldehyde **18**. The olefination afforded stereoselectively the all-*trans* isomer of pyrrhoxanthin **1** in 30 % yield, accompanied by the stereoisomeric mixture of β-hydroxyphosphonate intermediates (39 % yield), as confirmed by ^1H and ^{31}P NMR, HRMS (ESI^+), and IR spectroscopy. Subjecting this intermediate to the HWE reaction conditions led to the isolation of an additional 10 % yield of pyrrhoxanthin **1**. The configuration of the isolated norcarotenoid **1** was established through rigorous data analysis of the ^1H NMR spectra and comparison with those reported in the literature.[10] Attempts to improve the olefination yield by using longer reaction times, higher temperatures, or Barbier conditions led to degradation of the starting materials or products.

Conclusion

Enantiopure C_{37}-norcarotenoid pyrrhoxanthin has been prepared by a last-step stereoselective HWE condensation of C_{17}-phosphonate **15** and the C_{20}-aldehyde counterpart **18**. Highlights of the synthetic route are the silver-promoted lactonization of a pentenynoic acid to regio- and stereoselectively produce alkylidenebutyrolactones, and the Sonogashira reaction of C_6-difunctionalized phosphonate **17a** and enyne **16**. Importantly, the sensitive all-*trans* geometry of the oligoene was obtained with high stereocontrol and could be preserved in the final HWE condensation. Three different approaches to the stereoselective preparation of the γ-alkylidenebutenolide fragment were explored using functionalized vinylogous substrates with enyne, dienyne, and trienyne substructures. In all cases, the cyclization took place in high yields, which indicated that the procedure is robust and independent of the complexity and conjugation of the substrate, and delivers the desired fragment with high stereocontrol.

Experimental Section

General: Solvents were dried according to published methods and distilled before use except THF, CH_2Cl_2, CH_3CN, MeOH, Et_2O, and DMF which were dried using a Puresolv solvent purification system. All other reagents were commercial compounds of the highest purity available. All reactions were carried out under an argon atmosphere and those not involving aqueous reagents were carried out in oven-dried glassware. All solvents and anhydrous solutions were transferred through syringes and cannulae previously dried in the oven for at least 12 h and kept in a dessicator with KOH. Et_3N, acetone, iPr_2NH, *N,N*-diisopropylethylamine (DIPEA), and pyridine were dried by distillation with CaH_2. Distillations were carried out in a Büchi GKR-50 Kügelrohr and in that case the boiling points indicate the external temperature. For fractional distillations a microstill was used with an internal thermometer in the distillation head. The *n*BuLi concentration was determined by titration in triplicate with diphenylacetic acid or *N*-pivaloyl-*o*-toluidine in THF. For reactions at low temperature, ice/water or CO_2/acetone systems were used. For different temperatures, a HaaKe EK90 Immersion Cooler (−90 °C to −15 °C) was used. Analytical TLC analysis was performed on aluminum plates and visualized by UV irradiation (254 nm) or by staining with a solution of phosphomolibdic acid or anisaldehyde. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh), SilicaFlash P60 (230–400 mesh) or Merck Preparative C_{18} (125 Å, 55–105 μm) under pressure. Alternatively, a Biotage Horizon and an AnaLogix Intelliflash 310 HPFC Flash collector system were used. Melting points were measured in a Stuart Scientific apparatus. UV/VIS spectra were recorded with a Cary 100 Bio spectrophotometer in MeOH. IR spectra were obtained with a JASCO FTIR 4200 spectrophotometer, from a thin film deposited onto NaCl glass or with an ATR-module (Attenuated Total Reflectance). Specific rotations were measured on a JASCO P-1020 polarimeter with a Na lamp. HPLC was performed using a Waters instrument by using a dual wave detector. EIMS were recorded with a GC-TOF instrument (Waters Micromass). HRMS (ESI^+) were measured with an Apex III FTICR mass spectrometer (Bruker Daltonics). ^1H NMR spectra were recorded in $CDCl_3$, C_6D_6, and $(CD_3)_2CO$ at ambient temperature on a Bruker AMX-400 spectrometer operating at 400.16 MHz with residual protic solvent as the internal reference ($CDCl_3$, $\delta = 7.26$ ppm; C_6D_6, $\delta = 7.16$ ppm; $(CD_3)_2CO$, $\delta = 2.05$ ppm); chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows: δ (multiplicity, coupling constant J, number of protons). ^{13}C NMR spectra were recorded in $CDCl_3$, C_6D_6, and $(CD_3)_2CO$ at ambient temperature on the same spectrometer operating at 101.62 MHz with the central peak of $CDCl_3$ ($\delta_C = 77.2$ ppm), C_6D_6 ($\delta_C = 128.0$ ppm), and $(CD_3)_2CO$ ($\delta_C = 29.8$ ppm) as the internal reference. A DEPT-135 pulse sequence was used to aid in the assignment of signals in the ^{13}C NMR spectra. Crystallographic data were collected on a Bruker Smart 1000 CCD diffractometer at 20 °C by using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), and were corrected for Lorentz and polarization effects.

C_{20}-alcohol 29:[51] TAS-F (0.36 mL, 1 M in DMF, 0.36 mmol) was added to a cooled (0 °C) solution of C_{20}-*tert*-butyldimethylsilyloxy-lactone **28** (0.105 g, 0.18 mmol) in CH_3CN (11.3 mL). After stirring for 6 h at 0 °C, the reaction mixture was neutralized with a pH 7 phosphate buffer and then extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 95:5 to 90:10 CH_2Cl_2/MeOH) to afford a yellow solid (0.023 g, 37 %) identified as C_{20}-alcohol **29**. $[\alpha]_D^{24} = -94.50\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.9$ in MeOH); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.19$ (d, $J = 15.6$ Hz, 1H; H_7), 7.04 (s, 1H; H_{10}), 6.37 (d,

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$J=15.6$ Hz, 1H; H_8), 5.97 (tt, $J=6.6$, 1.3 Hz, 1H; H_{14}), 5.65 (s, 1H; H_{12}), 4.35 (d, $J=6.7$ Hz, 2H; H_{15}), 3.90 (dddd, $J=10.6$, 8.6, 5.1, 3.5 Hz, 1H; H_3), 2.39 (ddd, $J=14.3$, 5.0, 1.8 Hz, 1H; H_4), 2.09 (d, $J=1.1$ Hz, 3H; C_{13}-CH_3), 1.67–1.60 (m, 2H; H_4+H_2), 1.27–1.24 (m, 1H; H_2), 1.20 (s, 3H; CH_3), 1.195 (s, 3H; CH_3), 0.97 ppm (s, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): $\delta=168.8$ (s), 146.8 (s), 137.1 (d), 137.1 (d), 134.4 (d), 134.0 (s), 126.0 (s), 121.6 (d), 117.8 (d), 70.5 (s), 67.7 (s), 64.3 (d), 59.6 (t), 47.2 (t), 41.0 (t), 35.4 (s), 29.6 (q), 25.0 (q), 20.0 (q), 15.6 ppm (q); IR (NaCl): $\tilde{\nu}=3400$–3000 (w, O–H), 2962 (w, C–H), 2927 (w, C–H), 2870 (w, C–H), 1751 cm^{-1} (s, C=O); UV (MeOH): $\lambda_{max}=347$, 231 nm; HRMS (ESI$^+$): m/z: calcd. for $C_{20}H_{27}O_5$: 347.1853 $[M+H^+]$; found: 347.1854.

3-(Triisopropylsilyl)prop-2-yn-1-ol (31): *n*BuLi (7.3 mL, 1.49 M in hexane, 4.91 mmol) was added to a solution of ethynyltriisopropylsilane (**30**) (1.0 mL, 4.46 mmol) in THF (5.4 mL) at −20 °C. After stirring for 30 min, the reaction was cooled down to −78 °C and a suspension of HCHO (0.2 g, 6.69 mmol) in THF (6.7 mL) was added. After stirring for 15 h at 25 °C, brine was added and the mixture was extracted with ether (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 85:15, hexane/EtOAc) to afford a pale-yellow oil (0.90 g, 95 %) identified as **31**. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta=4.29$ (s, 2H; H_1), 1.06 ppm (s, 21H; $6\times CH_3+3\times CH$); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): $\delta=105.8$ (s), 87.0 (s), 51.9 (t), 18.7 (q, 6×), 11.3 ppm (d, 3×); IR (NaCl): $\tilde{\nu}=3500$–3000 (m, O–H), 2957 (s, C–H), 2944 (m, C–H), 2892 (s, C–H), 2867 (s, C–H), 2172 (w, C≡C), 1464 (s), 1040 cm^{-1} (s); MS (ESI$^+$): m/z (%): 235 $[M+Na]^+$ (57), 213 $[M+H]^+$ (100), 198 (77); HRMS (ESI$^+$): m/z calcd for $C_{12}H_{25}OSi$: 213.1669 $[M+H]^+$; found: 213.1677.

3-(Triisopropylsilyl)propiolaldehyde (22): A solution of 3-(triisopropylsilyl)prop-2-yn-1-ol (**31**) (0.68 g) in CH_2Cl_2 (6.5 mL) was added to a cooled (0 °C) 1:1 mixture of PCC and silica gel (1.12 g, 5.22 mmol) in CH_2Cl_2 (3.0 mL). After stirring for 6 h at 25 °C, the reaction was filtered through a pad of silica gel (CH_2Cl_2) to afford a pale-yellow oil (0.62 g, 92 %) identified as **22**, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta=9.20$ (s, 1H; H_1), 1.14–1.06 ppm (m, 21H; $6\times CH_3+3\times CH$); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): $\delta=176.8$ (d), 104.6 (s), 101.0 (s), 18.6 (q, 6×), 11.1 ppm (d, 3×); IR (NaCl): $\tilde{\nu}=2946$ (s, C–H), 2973 (m, C–H), 2868 (s, C–H), 2149 (w, C≡C), 1669 (s, C=O), 1000 cm^{-1} (s); MS (ESI$^+$): m/z (%): 233 (100) $[M+Na^+]$, 227 (22), 211 (10) $[M+H^+]$; HRMS (ESI$^+$): m/z: calcd for $C_{12}H_{23}OSi$: 211.1513 $[M<M+H]^+$; found: 211.1512.

Ethyl (*E*)-2-bromo-5-(triisopropylsilyl)pent-2-en-4-ynoate (33): [18]Crown-6 (0.92 g, 3.48 mmol) in a 1:1 THF/CH_3CN solvent mixture (16.0 mL) was added to a solution of phosphonate **32** (1.3 g, 3.2 mmol) in THF (8.0 mL). The resulting solution was cooled down to −78 °C and KHMDS (6.1 mL, 0.5 M in toluene, 3.04 mmol) was added. After stirring for 30 min at −78 °C, a solution of **22** (0.6 g, 2.9 mmol) in THF (1.6 mL) was added and stirring was maintained for 1 h at −78 °C. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 97:3 hexane/Et_3N) to afford a yellow oil (0.9 g, 86 %) identified as **33**. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta=6.23$ (s, 1H; H_3), 3.91 (q, $J=7.0$ Hz, 2H), 1.13 (s, 21H; $6\times CH_3+3\times CH$), 0.89 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6, 25 °C): $\delta=161.2$ (s), 125.0 (s), 123.1 (d), 104.4 (s), 102.7 (s), 62.3 (t), 18.8 (q, 6×), 14.0 (d, 3×), 11.6 ppm (q); IR (NaCl): $\tilde{\nu}=2944$ (s, C–H), 2893 (m, C–H), 2866 (s, C–H), 1727 (s, C=O), 1215 cm^{-1}(s); MS (ESI$^+$): m/z (%): 383 $[M(^{81}Br)+Na^+]$, 381 (98) $[M(^{79}Br)+Na^+]$, 361 (52) $[M(^{81}Br)+H^+]$, 359 $[M(^{79}Br)+H^+]$ (45); HRMS (ESI$^+$): m/z: calcd for $C_{16}H_{28}{}^{81}BrO_2Si$: 361.1018 $[M+H]^+$; found: 361.1005; calcd. for $C_{16}H_{28}{}^{79}BrO_2Si$: 359.1037 $[M+H]^+$; found: 359.1027.

(*Z*)-3-Bromo-1′-(triisopropylsilylmethylene)-5*H*-furan-2-one (34): LiOH (7.5 mL, 1 M in H_2O, 7.5 mmol) was added to a solution of ethyl (*E*)-2-bromo-5-(triisopropylsilyl)pent-2-en-4-ynoate (**33**) (0.90 g, 2.5 mmol) in THF (23.6 mL). After stirring for 6 h at 25 °C, EtOAc was added and the mixture was cooled down to 0 °C, neutralized with a 10 % aqueous solution of citric acid and then extracted with EtOAc (3×). The combined organic layers were washed with H_2O (2×) and brine (3×) and then dried (Na_2SO_4). The solvent was evaporated to afford (*E*)-2-bromo-1′-(triisopropylsilyl)pent-2-en-4-ynoic acid (**21**), which was used without further purification. $AgNO_3$ (0.76 g, 4.51 mmol) was added to a solution of this residue (0.83 g, 2.65 mmol) in MeOH (39.8 mL) and the reaction mixture was stirred for 41 h at 40 °C. The resulting mixture was filtered through a pad of Celite washing with EtOAc and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 80:20 hexane/EtOAc) to afford a pale-yellow oil (0.54 g, 68 %) identified as **34**. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta=7.40$ (s, 1H; H_4), 5.35 (s, 1H; $H_{1'}$), 1.36–1.21 (m, 3H; 3×CH), 1.07 ppm (d, $J=7.4$ Hz, 18H; $6\times CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): $\delta=166.1$ (s), 157.8 (s), 141.9 (d), 114.8 (s), 113.2 (d), 18.8 (q, 6×), 11.6 ppm (d, 3×); IR (NaCl): $\tilde{\nu}=2943$ (s, C–H), 2890 (m, C–H), 2866 (s, C–H), 1782 (s, C=O), 1624 (m), 1463 cm^{-1} (m); UV (MeOH): $\lambda_{max}=291$ nm; HRMS (ESI$^+$): m/z: calcd for $C_{14}H_{24}{}^{81}BrO_2Si$: 333.0703 $[M+H]^+$; found: 333.0697; calcd for $C_{16}H_{24}{}^{79}BrO_2Si$: 331.0724 $[M+H]^+$; found: 331.0718.

C_{16}-silane 35: **General procedure for the Stille coupling by using Fürstner-type conditions**: A degassed solution of stannane **7** (0.26 g, 0.55 mmol) and **34** (0.16 g, 0.48 mmol) in DMF (4.8 mL) was transferred to a flask containing flame-dried $[NBu_4][Ph_2PO_2]$ (0.28 g, 0.60 mmol). CuTC (0.046 g, 0.24 mmol) was added followed by $[Pd(PPh_3)_4]$ (0.055, 0.048 mmol) and the reaction was stirred for 1.5 h at 25 °C. The mixture was filtered through a pad of Celite and washed with EtOAc. The combined organic layers were washed with water (3×), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, from 80:20 to 70:30 hexane/EtOAc) to afford a pale-yellow solid (0.105 g, 51 %) identified as C_{16}-silane **35**. M.p. 102–105 °C (hexane); $[\alpha]_D^{24}=-83.33\ cm^3\,g^{-1}\,dm^{-1}$ ($c=1.0$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta=7.53$ (d, $J=15.6$ Hz, 1H; H_7), 6.48 (d, $J=15.6$ Hz, 1H; H_8), 6.07 (s, 1H; H_{10}), 4.86 (s, 1H; H_{12}), 3.80–3.70 (m, 1H; H_3), 2.20 (dd, $J=14.3$, 5.0 Hz, 1H), 1.47–1.39 (m, 2H), 1.29–1.20 (m, 3H; 3×CH), 1.18–1.00 ppm (m, 27H; $9\times CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): $\delta=168.9$ (s), 159.5 (s), 136.5 (d), 135.8 (d), 128.6 (s), 122.0 (d), 109.4 (d), 70.4 (s), 67.5 (s), 63.9 (d), 47.3 (t), 41.2 (t), 35.3 (s), 29.5 (q), 25.3 (q), 20.0 (q), 19.0 (q, 6×), 11.9 ppm (d, 3×); IR (NaCl): $\tilde{\nu}=3600$–3100 (w, O–H), 2941 (s, C–H), 2866 (m, C–H), 1768 (s, C=O), 1618 (m), 1049 cm^{-1}(m); UV (MeOH): $\lambda_{max}=312$, 231 nm; HRMS (ESI$^+$): m/z: calcd for $C_{25}H_{41}O_4$: 433.2769 $[M+H]^+$; found: 433.2759.

C_{16}-iodide 36: Ag_2CO_3 (0.069 g, 0.116 mmol) and NIS (0.036 g, 0.162 mmol) were added to a cooled (−7 °C) solution of C_{16}-silane **35** (0.054 g, 0.125 mmol) in HFIP (0.6 mL). After stirring for 25 h at −7 °C, water was added and the reaction mixture was extracted with EtOAc (3×), dried (Na_2SO_4), filtered through a pad of Celite, and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 68:30:2 to 50:50:0 hexane/EtOAc/Et_3N) to afford C_{16}-iodide **36** as a pale-yellow oil (0.044 g, 88 %). $[\alpha]_D^{24}=-79.20\ cm^3\,g^{-1}\,dm^{-1}$ ($c=0.8$ in MeOH); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta=7.46$ (d, $J=15.6$ Hz, 1H; H_7), 6.27 (d, $J=15.6$ Hz, 1H; H_8), 5.67 (s, 1H; H_{10}), 5.18 (s, 1H; H_{12}), 3.83–3.71 (m, 1H; H_3), 2.20 (app. ddd, $J=14.3$, 5.0, 1.7 Hz, 1H; H_{4A}), 1.48–1.39 (m, 2H; $H_{4B}+H_{2A}$), 1.09–1.06 (m, 1H; H_{2B}), 1.07 (s, 3H; C_1–CH_3), 1.03 (3s, 3H; C_1–CH_3), 1.02 ppm (s, 3H; C_5–CH_3); ^{13}C NMR (101 MHz, C_6D_6, 25 °C): $\delta=167.2$ (s), 155.9 (s), 136.8 (d), 132.6 (d), 128.6 (s), 121.7 (d), 70.5 (s), 67.5 (s), 63.8 (d), 61.6 (d), 47.2 (t), 41.1 (t), 35.2 (s), 29.4 (q), 25.3 (q), 19.8 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3100 (br, O–H), 2960 (s, C–H), 2926 (m, C–H), 2855 (m, C–H), 1776 (s, C=O), 1711 (m), 1044 cm^{-1} (m); UV (MeOH): $\lambda_{max}=328$, 241 nm; HRMS (ESI$^+$): m/z: calcd for $C_{16}H_{19}IO_4$: 403.0401 $[M+H]^+$; found: 403.0399.

C_{20}-alcohol 29: Following the described procedure for the Stille coupling using Fürstner-type conditions, the reaction of C_{16}-iodide **36** (0.018 g, 0.045 mmol), stannane **37** (0.018 g, 0.051 mmol), $[NBu_4][Ph_2PO_2]$ (0.026 g, 0.056 mmol), CuTC (0.004 g, 0.022 mmol), and $[Pd(PPh_3)_4]$ (0.005, 4.5×10^{-3} mmol) in DMF (1.3 mL) afforded after purification by column chromatography (silica gel, from 90:10 to 70:30 CH_2Cl_2/acetone) a yellow solid (0.014 g, 90 %) identified as C_{20}-alcohol **29**.

C_{14}-silane 39b: Cs_2CO_3 (0.25 g, 0.77 mmol), CuCl (0.004 g, 0.04 mmol), $Pd(OAc)_2$ (0.013 g, 0.019 mmol), and dppf (0.02 g, 0.039 mmol) and a solution of boronate **24** (0.17 g, 0.58 mmol) in DMF (2.5 mL) were sequentially added to a solution of iodide **38b** (0.16 g, 0.39 mmol) in DMF

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(1.5 mL). After stirring for 3 h at 25 °C, EtOAc was added. The organic layer was washed with H_2O (3×) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica C18, CH_3CN) to afford a colorless oil (0.11 g, 60 %) identified as C_{14}-silane **39b** and diethyl (2*Z*,3*Z*)-2,3-bis(trimethylsilylmethylidene)succinate (**40**) (0.032 g, 16 %) as a yellow oil.

*Data for C_{14}-silane **39b***: $[\alpha]_D^{25} = -61.60\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.7$ in MeOH); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 6.65$ (dd, $J = 15.6$, 0.8 Hz, 1H; H_8), 6.43 (d, $J = 15.6$ Hz, 1H; H_7), 6.08 (s, 1H; H_{10}), 4.09–3.94 (m, 3H; H_3 + $CO_2CH_2CH_3$), 2.28 (app. ddd, $J = 14.4$, 5.1, 1.7 Hz, 1H; H_{4A}), 1.63 (dd, $J = 14.4$, 8.3 Hz, 1H; H_{4B}), 1.59 (app. ddd, $J = 13.1$, 3.4, 1.6 Hz, 1H; H_{2A}), 1.28 (dd, $J = 13.0$, 10.0 Hz, 1H; H_{2B}), 1.14 (s, 3H; CH_3), 1.11 (s, 3H; CH_3), 1.09 (s, 3H; CH_3), 0.98 (s, 9H; 3×CH_3), 0.97 (s, 3H; CH_3), 0.19 (s, 9H; 3×CH_3), 0.06 (s, 3H; CH_3), 0.05 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): $\delta = 167.8$ (s), 146.0 (s), 141.0 (d), 133.2 (d), 129.7 (d), 70.0 (s), 66.9 (s), 65.2 (d), 60.7 (t), 47.8 (t), 42.0 (t), 35.5 (s), 29.5 (q), 26.1 (q, 3×), 25.3 (q), 20.2 (q), 18.3 (q), 14.2 (q), −0.4 (q, 3×), −4.5 ppm (q); IR (NaCl): $\tilde{\nu} = 2956$ (m, C−H), 2929 (m, C−H), 2857 (w, C−H), 1724 (s, C=O), 1250 cm^{-1}(s); MS (ESI$^+$): *m*/*z* (%): 489 [*M*+Na$^+$] (13), 467 [*M*+H$^+$] (100); HRMS (ESI$^+$): *m*/*z*: calcd for $C_{25}H_{47}O_4Si_2$: 467.3007 [*M*+H]$^+$; found: 467.3021.

*Data for **40***: ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 6.54$ (s, 2×1H), 3.96 (q, $J = 7.1$ Hz, 4H; 2×$CO_2CH_2CH_3$), 0.93 (t, $J = 7.1$ Hz, 6H, 2×$CO_2CH_2CH_3$), 0.32 ppm (s, 18H, 6×CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): $\delta = 166.7$ (s, 2×), 149.1 (s, 2×), 146.5 (d, 2×), 60.8 (t, 2×), 14.1 (q, 2×), −0.3 ppm (q, 6×); IR (NaCl): $\tilde{\nu} = 2957$ (m, C−H), 1726 (s, C=O), 854 cm^{-1} (s); MS (ESI$^+$): *m*/*z* (%): 365 (100) [*M*+Na$^+$], 343 (46) [*M*+H$^+$], 297 (11), 249 (8); HRMS (ESI$^+$): *m*/*z*: calcd for $C_{16}H_{31}O_4Si_2$: 343.1755 [*M*+H]$^+$; found: 343.1748.

C_{14}-iodide 41b: 2,6-Lutidine (0.013 mL, 0.11 mmol) and NIS (0.054 g, 0.24 mmol) were added to a cooled (0 °C) solution of silane **39b** (0.074 g, 0.16 mmol) in (HFIP, 1.6 mL). After the reaction mixture had been stirred for 2.5 h at 0 °C, water and Et_2O were added, the layers were separated, and the organic layer was washed with a saturated aqueous solution of $Na_2S_2O_3$ (1×), water (1×), and a saturated aqueous solution of $NaHCO_3$ (1×), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica C18, CH_3CN) to afford a pale-yellow oil (0.068 g, 81 %) identified as C_{14}-iodide **41b**. $[\alpha]_D^{25} = -58.20\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.9$ in MeOH); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 6.30$ (d, $J = 15.7$ Hz, 1H; H_8), 6.16 (d, $J = 15.7$ Hz, 1H; H_7), 6.04 (s, 1H; H_{10}), 4.18–4.09 (m, 2H; $CO_2CH_2CH_3$), 3.97 (dddd, $J = 9.9$, 8.3, 5.0, 3.4 Hz, 1H; H_3), 2.25 (app. ddd, $J = 14.4$, 5.1, 1.7 Hz, 1H; H_{4A}), 1.60 (dd, $J = 14.4$, 8.2 Hz, 1H; H_{4B}), 1.55 (app. ddd, $J = 11.4$, 3.2, 1.6 Hz, 1H; H_{2A}), 1.25 (dd, $J = 13.0$, 10.0 Hz, 1H; H_{2B}), 1.06 (s, 3H; C_5-CH_3), 1.05 (s, 3H; C_1-CH_3), 1.02 (s, 3H; C_1-CH_3), 1.01 (s, 3H; $CO_2CH_2CH_3$), 0.98 (s, 9H; 3×CH_3), 0.06 (s, 3H; CH_3), 0.05 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): $\delta = 167.0$ (s), 145.6 (s), 130.3 (d), 130.1 (d), 82.6 (d), 69.9 (s), 67.0 (s), 65.1 (d), 61.0 (t), 47.6 (t), 41.8 (t), 35.2 (s), 29.3 (q), 26.1 (q, 3×), 25.2 (q), 20.0 (q), 18.3 (s), 14.2 (q), −4.6 ppm (q, 2×); IR (NaCl): $\tilde{\nu} = 2956$ (s, C−H), 2928 (s, C−H), 2856 (m, C−H), 1733 (s, C=O), 1183 cm^{-1}(s); HRMS (ESI$^+$): *m*/*z*: calcd for $C_{22}H_{38}IO_4Si$: 521.1579 [*M* < M + H]$^+$; found: 521.1575.

C_{20}-alcohol 42b: Alkyne **14** (0.018 g, 0.19 mmol), [Pd(PPh$_3$)$_4$] (0.014 g, 0.012 mmol), and CuI (0.002 g, 0.012 mmol) were sequentially added to a stirred solution of iodide **41b** (0.065 g, 0.13 mmol) in *i*Pr$_2$NH (1.5 mL) at 25 °C. After stirring for 1 h at 25 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and the mixture was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica-NH_2, 85:15 hexane/EtOAc) to afford a colorless oil (0.047 g, 77 %) identified as C_{20}-alcohol **42b**. $[\alpha]_D^{26} = -67.7\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.2$ in MeOH); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): $\delta = 6.52$ (d, $J = 15.6$ Hz, 1H; H_7 or H_8), 6.47 (d, $J = 15.6$ Hz, 1H; H_7 or H_8), 6.04 (tq, $J = 6.5$, 1.5 Hz, 1H; H_{14}), 5.73 (s, 1H; H_{10}), 4.21–4.07 (m, 2H; $CO_2CH_2CH_3$), 3.98 (dddd, $J = 10.0$, 8.4, 5.0, 3.3 Hz, 1H; H_3), 3.83 (d, $J = 6.6$ Hz, 2H; 2H$_{15}$), 2.27 (app. ddd, $J = 14.4$, 5.1, 1.6 Hz, 1H; H_{4A}), 1.65–1.54 (m, 2H; H_{2A} + H_{4B}), 1.61 (s, CH_3), 1.27 (dd, $J = 13.0$, 10.1 Hz, 1H; H_{2B}), 1.09 (s, 3H; CH_3), 1.08 (s, 3H; CH_3), 1.07 (s, 3H; CH_3), 1.06 (s, 3H; CH_3), 0.98 (s, 9H; 3×CH_3), 0.06 (s, 3H; CH_3), 0.05 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): $\delta = 166.4$ (s), 141.6 (s), 138.4 (d), 131.5 (d), 130.1 (d), 120.1 (s), 114.6 (d), 102.0 (s), 85.7 (s), 70.2 (s), 67.2 (s), 65.2 (d), 60.9 (t), 59.1 (t), 47.7 (t), 41.9 (t), 35.4 (s), 29.4 (q), 26.1 (q, 3×), 25.3 (q), 20.1 (q), 18.3 (s), 17.3 (q), 14.4 (q), −4.6 ppm (q, 2×); IR (NaCl): $\tilde{\nu} = 3600$–3000 (br, O−H), 2956 (s, C−H), 2928 (s, C−H), 2856 (m, CH), 2181 (w, C≡C), 1722 (s, C=O), 1379 (s), 1084 cm^{-1}(s); MS (ESI$^+$): *m*/*z* (%): 511 [*M*+Na$^+$] (14), 489 [*M*+H$^+$] (100); HRMS (ESI$^+$): *m*/*z*: calcd for $C_{28}H_{45}O_5Si$: 489.3031 [*M*+H]$^+$; found: 489.3043.

C_{20}-lactone 43: A solution of alcohol **42b** (0.02 g, 0.041 mmol) in ethanol (0.20 mL) was added to a mixture of a 2 N aqueous solution of KOH (0.16 mL) and ethanol (0.66 mL) at 70 °C. After stirring for 30 min at 70 °C, the reaction was cooled down to 0 °C and diethyl ether was added. The pH was adjusted to 7 with DOWEX 50WX8, the mixture was filtered through a pad of Celite (Et_2O) and the solvent was evaporated. The crude was purified by crystallization (hexane/Et_2O) to afford a white solid identified as C_{20}-acid **23** (16.4 mg, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 6.40$ (d, $J = 15.7$ Hz, 1H; H_7), 6.28 (d, $J = 15.6$ Hz, 1H; H_8), 6.10 (s, 1H; H_{10}), 6.06 (t, $J = 6.4$ Hz, 1H; H_{14}), 4.26 (d, $J = 6.7$ Hz, 2H; H_{15}), 3.87–3.80 (m, 1H; H_3), 2.24 (dd, $J = 14.4$, 5.1 Hz, 1H; H_{4A}), 1.85 (s, 3H; CH_3), 1.64 (dd, $J = 14.4$, 8.3 Hz, 1H; H_{4B}), 1.54–1.45 (m, 1H; H_{2A}), 1.30–1.18 (m, 1H: H_{2B}), 1.17 (s, 3H; CH_3), 1.12 (s, 3H; CH_3), 0.95 (s, 3H; CH_3), 0.87 (s, 9H; 3×CH_3), 0.04 ppm (s, 6H; 2×CH_3).

$AgNO_3$ (0.008 g, 0.048 mmol) was added to a solution of acid **23** (0.004 g, $8.7\cdot10^{-3}$ mmol) in MeOH (0.4 mL). After stirring for 1 h at 25 °C, the reaction mixture was filtered through a pad of silica gel (hexane/EtOAc) and the solvent was evaporated to afford a pale-yellow solid (0.004 g, 100 %) identified as C_{20}-lactone **43**. M.p. 139–140 °C (hexane/EtOAc); $[\alpha]_D^{24} = -64.1\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.1$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.19$ (d, $J = 15.6$ Hz, 1H; H_7), 7.03 (s, 1H; H_{10}), 6.35 (d, $J = 15.5$ Hz, 1H; H_8), 5.96 (tq, $J = 6.6$, 1.0 Hz, 1H; H_{14}), 5.64 (s, 1H; H_{12}), 4.35 (d, $J = 6.6$ Hz, 2H; H_{15}), 3.85 (dddd, $J = 10.1$, 8.4, 5.1, 3.4 Hz, 1H; H_3), 2.25 (app. ddd, $J = 14.5$, 5.1, 1.6 Hz, 1H; H_{4A}), 2.09 (d, $J = 0.9$ Hz, 3H; C_{13}-CH_3), 1.69–1.65 (m, 1H; H_{4B}), 1.51 (app. ddd, $J = 13.2$, 3.4, 1.6 Hz, 1H; H_{2A}), 1.27–1.24 (m, 1H; H_{2B}), 1.18 (s, 3H; C_1-CH_3), 1.17 (s, 3H; C_5-CH_3), 0.94 (s, 3H; C_1-CH_3), 0.88 (s, 9H; 3×CH_3), 0.05 (s, 3H; CH_3), 0.045 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta =$ 168.8 (s), 146.8 (s), 137.0 (d), 136.9 (d), 134.8 (d), 134.2 (s), 126.2 (s), 121.4 (d), 117.7 (d), 70.7 (s), 67.7 (s), 64.8 (d), 59.7 (t), 47.1 (t), 41.5 (t), 35.3 (s), 29.6 (q), 26.0 (q), 25.1 (q), 20.2 (q), 18.3 (s), 15.7 (q), −4.57 (q), −4.61 ppm (q); IR (NaCl): $\tilde{\nu} = 3700$–3500 (br, OH), 2955 (s, C−H), 2927 (s, C−H), 2855 (s, C−H), 1757 cm^{-1}(s, C=O); MS (ESI$^+$): *m*/*z* (%): 483 (19) [*M*+Na$^+$], 461 (100) [*M*+H$^+$]; HRMS (ESI$^+$): *m*/*z*: calcd for $C_{26}H_{41}O_5Si$: 461.2718 [*M*+H$^+$]; found: 461.2728.

C_{20}-alcohol 29: A cooled (0 °C) mixture of THF/HCO_2H/H_2O (2.7 mL, 6:3:1 ratio) was added to a cooled (0 °C) flask containing C_{20}-lactone **43** (0.029 g, 0.063 mmol). After stirring for 6 h at 0 °C, EtOAc was added and the reaction mixture was neutralized at 0 °C with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×), the organic layer was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 95:5 to 90:10 CH_2Cl_2/MeOH) to afford a yellow solid (0.016 g 74 %) identified as C_{20}-alcohol **29**.

C_{20}-aldehyde 18: Na_2CO_3 (0.40 g, 4.14 mmol) and MnO_2 (0.44 g, 4.14 mmol) were added to a cooled solution of C_{20}-alcohol **29** (0.080 g, 0.23 mmol) in CH_2Cl_2 (27.0 mL). After stirring for 30 min at 0 °C, the reaction mixture was filtered through a pad of Celite (80:20, CH_2Cl_2/MeOH) and the solvent was evaporated to afford a yellow solid (0.079 g, 93 %) identified as C_{20}-aldehyde **18**, which was used without further purification. $[\alpha]_D^{25} = -85.5\ cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.3$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 10.12$ (d, $J = 8.0$ Hz, 1H; H_{15}), 7.29 (d, $J = 15.8$ Hz, 1H; H_7), 7.07 (s, 1H; H_{10}), 6.42 (d, $J = 15.8$ Hz, 1H; H_8), 6.14 (d, $J = 8.0$ Hz, 1H; H_{14}), 5.72 (s, 1H; H_{12}), 3.96–3.86 (m, 1H; H_3), 2.55 (s, 3H; C_{13}-CH_3), 2.45–2.34 (m, 1H; H_{4A}), 1.69–1.59 (m, 2H; H_{4B} + H_{2A}), 1.31–1.23 (m, 1H; H_2), 1.20 (s, 3H; CH_3), 1.19 (s, 3H; CH_3), 0.96 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 191.2$ (d), 167.7 (s), 151.7 (s), 137.1 (d), 136.1 (d), 132.8 (d), 128.8 (s), 121.3 (d), 115.4 (d), 77.4 (s), 70.5 (s), 67.9 (s), 64.2 (d), 47.0 (t), 40.9 (t), 35.4 (s), 29.6 (q), 25.1

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(q), 20.0 (q), 16.4 ppm (q); IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, O–H), 3080 (w, C–H), 2963 (m, C–H), 2928 (m, C–H), 2865 (m, C–H), 1777 (s, C=O), 1657 (s, C=O), 1612 (m), 1040 cm^{-1}(s); UV (MeOH): λ_{max} = 355 nm; MS (ESI$^+$): *m*/*z* (%): 345 (100) [*M*+H$^+$]; HRMS (ESI$^+$): *m*/*z*: calcd for $C_{20}H_{25}O_5$: 345.1697 [*M*+H]$^+$; found: 345.1699.

(2*E*,4*E*)-5-Iodohexa-2,4-dien-1-ol (45): NIS (0.17 g, 0.74 mmol) was added to a solution of stannane **44** (0.22 g, 0.57 mmol) in CH_3CN (33.0 mL) and the reaction mixture was stirred for 1 h at 0 °C. A saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ were sequentially added and the mixture was extracted with Et_2O (3×). The organic layer was washed with water (3×) and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 80:17:3 to 65:35:0 hexane/EtOAc/Et_3N) to afford a colorless oil (0.12 g, 94%) identified as **45**. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 6.74–6.70 (m, 1H; H_4), 6.09 (ddt, *J* = 14.7, 11.0, 1.7 Hz, 1H; H_3), 5.33 (dt, *J* = 15.1, 5.2 Hz, 1H; H_2), 3.70 (d, *J* = 4.9 Hz, 2H; H_1), 2.17–2.15 ppm (m, 3H; CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 140.4 (d), 133.8 (d), 125.2 (d), 97.3 (s), 62.5 (t), 27.9 ppm (q); IR (NaCl): $\tilde{\nu}$ = 3500–3000 (br, O–H), 2913 (w, C–H), 2858 (w, C–H), 1091 (s), 962 cm^{-1} (s); MS (ESI$^+$): *m*/*z* (%): 247 (87) [*M*+Na$^+$], 207 (100), 203 (68), 201 (50); HRMS (ESI$^+$): *m*/*z*: calcd for C_6H_9INaO: 246.9590 [*M*+Na$^+$]; found: 246.9594.

Dimethyl (2*E*,4*E*)-5-iodohexa-2,4-dien-1-ylphosphonate (17b): 4-Dimethylaminopyridine (DMAP; 0.053 g, 0.43 mmol) and MsCl (0.055 mL, 0.72 mmol) were added dropwise to a solution of alcohol **45** (0.075 g, 0.33 mmol) in CH_2Cl_2 (4.5 mL). After stirring for 17 h at 25 °C, the reaction mixture was filtered through a pad of silica gel (washing with hexane), the solvent was evaporated, and the residue was used immediately without further purification. NaI (0.055 g, 0.37 mmol) was added to a solution of this residue in $P(OMe)_3$ (0.73 mL) and the reaction mixture was stirred for 4 h at 70 °C. The reaction mixture was poured into water, extracted with EtOAc (3×), and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (C-18 silica gel, CH_3CN) to afford a colorless oil (0.044 g, 42%) identified as **17b**. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 6.63 (d, *J* = 10.9 Hz, 1H, H_4), 5.96 (app. dddt, *J* = 15.0, 10.9, 1.4 Hz, $^3J_{P\text{-}H}$ = 5.0 Hz, 1H, H_3), 5.37 (app. ddt, *J* = 15.2, 7.6 Hz, $^2J_{P\text{-}H}$ = 7.6 Hz, 1H, H_2), 3.38–3.32 (m, 6H; 2×CH_3), 2.29 (dd, *J* = 7.6, $^1J_{P\text{-}H}$ = 22.6 Hz, 3H, 2H_1), 2.10 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 140.2 (d, $^4J_{C\text{-}P}$ = 4.8 Hz), 129.9 (d, $^3J_{C\text{-}P}$ = 14.6 Hz), 123.8 (d, $^2J_{C\text{-}P}$ = 12.1 Hz), 97.3 (s, $^5J_{C\text{-}P}$ = 5.9 Hz), 52.2 (q, $^2J_{C\text{-}P}$ = 6.4 Hz), 30.1 (t, $^1J_{C\text{-}P}$ = 139.9 Hz), 27.9 ppm (q).

Diethyl (2*E*,4*E*) 5-iodohexa-2,4-dien-1-yl-phosphonate (17a): $P(OEt)_3$ (0.58 mL) and then a solution of the alcohol **45** (0.25 g, 1.12 mmol) in THF (2.8 mL) were added to a solution of ZnI_2 (0.53 g, 1.67 mmol) in THF (1.0 mL). After the mixture had been stirred for 16 h at 85 °C, the solvent was evaporated and the residue was washed with a 2 M aqueous solution of NaOH and extracted with Et_2O. The organic layer was washed with brine (2×) and H_2O (2×), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 30:70 to 20:80 hexane/EtOAc) to afford a colorless oil (0.25 g, 70%) identified as **17a**. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 6.77 (d, *J* = 10.9 Hz, 1H; H_4), 6.09 (dddt, *J* = 15.1, 10.9, 1.4, $^3J_{P\text{-}H}$ = 5.0 Hz, 1H; H_3), 5.55 (ddt, *J* = 15.2, 7.6, $^2J_{P\text{-}H}$ = 7.6 Hz, 1H; H_2), 4.05–3.95 (m, 4H; 2×CH_2CH_3), 2.45 (dd, *J* = 7.6, $^1J_{P\text{-}H}$ = 22.5 Hz, 2H; H_1), 2.22 (d, *J* = 1.8 Hz, 3H; H_6), 1.12 ppm (t, *J* = 7.1 Hz, 6H; 2×CH_2CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 140.3 (d, $^4J_{C\text{-}P}$ = 4.80 Hz), 129.8 (d, $^3J_{C\text{-}P}$ = 14.6 Hz), 124.2 (d, $^2J_{C\text{-}P}$ = 12.2 Hz), 97.1 (s, $^5J_{C\text{-}P}$ = 5.9 Hz), 61.7 (t, $^2J_{C\text{-}P}$ = 6.4 Hz), 31.2 (t, $^1J_{C\text{-}P}$ = 139.9 Hz, 2×), 27.9 (q), 16.5 ppm (q, $^3J_{C\text{-}P}$ = 5.7 Hz, 2×); IR (NaCl): $\tilde{\nu}$ = 2980–2908 (w, C–H), 1246 (m, P=O), 1022 (s, P-O-C), 963 cm^{-1} (s, P-O-C); HRMS (ESI$^+$): *m*/*z*: calcd for $C_{10}H_{19}IO_3P$: 345.0111 [*M*+H]$^+$; found: 345.0115.

C_{16}-acetoxy-phosphonate 15: A degassed solution of the iodide **17a** (0.04 g, 0.11 mmol) in THF (1.3 mL), Et_3N (0.02 mL), and a degassed solution of the alkyne **16** (0.03 g, 0.15 mmol) in THF (1.3 mL) were sequentially added to a deoxygenated suspension of [Pd(PPh_3)$_4$] (0.004 g, 3.4×10^{-3} mmol) and CuI (0.002 g, 0.01 mmol) in THF (1.0 mL). After the mixture had been stirred for 24 h, the reaction mixture was filtered through a pad of Celite (washing with EtOAc) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 85:15 to 50:50 hexane/EtOAc) to afford a colorless oil (0.024 g, 56%) identified as **15**. $[\alpha]_D^{25}$ = −37.7 $cm^3 g^{-1} dm^{-1}$ (*c* = 0.5 in MeOH); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 6.50 (d, *J* = 11.4 Hz, 1H; H_{10}), 6.32 (dddt, *J* = 16.3, 11.4, 1.4, $^3J_{P\text{-}H}$ = 5.1 Hz, 1H; H_{11}), 5.66 (ddt, *J* = 15.5, 7.8, $^2J_{P\text{-}H}$ = 7.8 Hz, 1H; H_{12}), 5.17 (dddd, *J* = 11.4, 9.3, 5.7, 3.6 Hz, 1H; H_3), 3.96–3.86 (m, 4H; 2×CH_2CH_3), 2.47 (dd, *J* = 7.7, $^1J_{P\text{-}H}$ = 23.0 Hz, 2H; H_{13}), 2.32 (dd, *J* = 17.6, 5.4 Hz, 1H; H_{4A}), 2.00 (dd, *J* = 17.6, 9.0 Hz, 1H; H_{4B}), 1.84 (dd, *J* = 3.6, 1.8 Hz, 1H; H_{2A}), 1.82 (s, 6H; 2×CH_3), 1.82–1.80 (m, 1H; H_{2B}), 1.72 (s, 3H; CH_3), 1.26 (s, 3H; CH_3), 1.22 (s, 3H; CH_3), 1.06–1.00 ppm (m, 6H; 2×CH_2CH_3); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 169.7 (s), 136.7 (s), 134.3 (d, $^4J_{C\text{-}P}$ = 5.3 Hz), 130.8 (d, $^2J_{C\text{-}P}$ = 15.2 Hz), 124.8 (s), 124.6 (d, $^3J_{C\text{-}P}$ = 13.0 Hz), 119.3 (s, $^5J_{C\text{-}P}$ = 5.5 Hz), 98.2 (s, $^6J_{C\text{-}P}$ = 3.3 Hz), 88.3 (s), 67.9 (d), 61.7 (t, $^2J_{C\text{-}P}$ = 6.5 Hz), 42.7 (t), 37.7 (t), 36.4 (s), 31.8 (t, $^1J_{C\text{-}P}$ = 139.2 Hz; 2×OCH_2CH_3), 30.5 (q), 28.8 (q), 22.4 (q), 21.0 (q), 18.0 (q), 16.6 ppm (q, $^2J_{C\text{-}P}$ = 5.6 Hz; 2×OCH_2CH_3); IR (NaCl): $\tilde{\nu}$ = 2966 (w, C–H), 2928 (w, C–H), 1732 (s, C=O), 1243 (s), 1025 cm^{-1} (s); MS (ESI$^+$): *m*/*z* (%): 445 (100) [*M*+Na$^+$], 423 (9), 363 (14), 227 (56); HRMS (ESI$^+$): *m*/*z* calcd for $C_{23}H_{35}NaO_5P$: 445.2114 [*M*+Na]$^+$; found: 445.2103.

Pyrrhoxanthin (1): NaHMDS (1.0 M solution in THF, 0.117 mL, 0.117 mmol) was added dropwise to a cold (−78 °C) solution of C_{16}-acetoxy-phosphonate **15** (0.024 g, 0.057 mmol) in THF (2.4 mL). After the mixture had been stirred for 10 min at −78 °C, a solution of C_{20}-aldehyde **18** (0.018 g, 0.053 mmol) in THF (2.4 mL) was added slowly. After stirring for 15 min at −78 °C, a pH 7 phosphate buffer was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (MPLC, CN silica gel, from 95:5 to 85:15 hexane/acetone) to afford a reddish oil (0.010 g, 30%) identified as **1**. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 7.56 (d, *J* = 15.5 Hz, 1H; H_7), 6.67 (d, *J* = 11.4 Hz, 1H; $H_{10'}$), 6.56 (d, *J* = 15.5 Hz, 1H; H_8), 6.50–6.40 (m, 2H; H_{15}+$H_{11'}$), 6.33–6.27 (m, 2H; H_{14}+$H_{15'}$), 6.19–6.12 (m, 1H; $H_{14'}$), 6.15 (s, 1H; H_{10}), 5.22–5.14 (m, 1H; $H_{3'}$), 5.19 (s, 1H; H_{12}), 3.79–3.72 (m, 1H; H_3), 2.34 (dd, *J* = 17.6, 5.5 Hz, 1H; $H_{4'A}$), 2.20 (ddd, *J* = 14.2, 5.1, 1.5 Hz, 1H; H_{4A}), 2.12 (s, 3H; C_{13}-CH_3), 2.01 (ddd, *J* = 17.8, 9.1, 1.0 Hz, 1H; $H_{4'B}$), 1.90 (s, 3H; $C_{9'}$-CH_3), 1.85 (s, 3H; $C_{5'}$-CH_3), 1.84 (ddd, *J* = 40 3.5, 1.6 Hz, 1H; $H_{2'A}$), 1.72 (s, 3H; $COCH_3$), 1.58–1.51 (m, 1H; $H_{2'B}$), 1.42 (dd, *J* = 14.3, 8.8 Hz, 1H; H_{4B}), 1.42 (ddd, *J* = 12.9, 3.4, 1.4 Hz, 1H; H_{2A}), 1.30 (s, 3H; $C_{1'}$-CH_3), 1.26 (s, 3H; $C_{1'}$-CH_3), 1.12 (s, 3H; C_1-CH_3), 1.08 (s, 3H; C_1-CH_3), 1.07 (s, 3H; C_5-CH_3), 1.10–1.02 ppm (m, 1H; H_{2B}); ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 169.7 (s), 168.3 (s), 147.6 (s), 137.5 (s), 137.3 (d), 136.8 (d), 136.3 (d), 135.2 (d), 134.8 (d), 134.7 (s), 134.5 (d), 130.6 (d), 130.5 (d), 125.2 (s), 124.9 (d), 122.4 (d), 121.2 (s), 118.4 (d), 99.2 (s), 90.8 (s), 70.5 (s), 67.8 (s), 67.5 (d), 63.9 (d), 47.3 (t), 42.7 (t), 41.2 (t), 37.7 (t), 36.4 (s), 35.3 (s), 30.5 (q), 29.5 (q), 28.9 (q), 25.3 (q), 22.5 (q), 20.9 (q), 19.9 (q), 18.2 (q), 15.6 ppm (q); HRMS (ESI$^+$): *m*/*z*: calcd for $C_{39}H_{49}O_6$: 613.3524 [*M*+H]$^+$; found: 613.3519.

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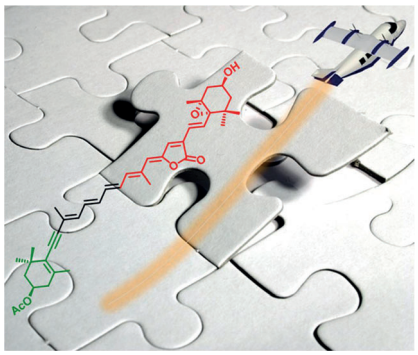
Silver catalysis: A stereocontrolled total synthesis of enantiopure pyrrhoxanthin has been described (see scheme), using a Horner–Wadsworth–Emmons (HWE) condensation as the last step, providing the desired xanthophyll as a single diastereomer. Along this strategy, alkylidenebutyrolactones have been obtained regio- and stereoselectively by silver-promoted lactonization of pentenynoic acids of increasing complexity.



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Total Synthesis of Enantiopure Pyrrhoxanthin: Alternative Methods for the Stereoselective Preparation of 4-Alkylidenebutenolides

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