Carotenoids

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Total Synthesis of Naturally Configured Pyrrhoxanthin, a Carotenoid Butenolide from Plankton**

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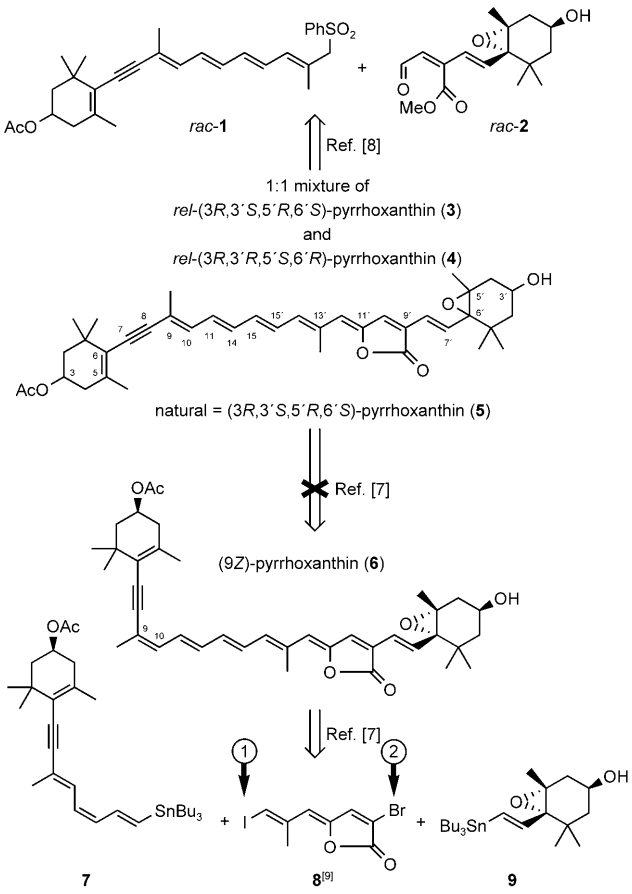
The structure[1] of the marine natural product pyrrhoxanthin (**5**) is highly unusual for a carotenoid.[2] Firstly, it comprises 37 rather than 40 carbon atoms, and secondly it contains oxygen substituents not only in the six-membered rings but as constituents of an annulated butenolide. Pyrrhoxanthin has been isolated from the chloroplasts of various dinoflagellates[3] and usually accompanies the more abundantly encountered C_{37}-butenolide carotenoid peridinin.[4] Because of its low concentration in biological sources and its instability after purification little is known about the properties of pyrrhoxanthin. It is not known, for instance, whether pyrrhoxanthin participates in photosynthesis in plankton as peridinin does.[5]

In a rigorous sense pyrrhoxanthin (**5**) has not yet been synthesized in the laboratory (Scheme 1). This is somewhat surprising because four total syntheses of peridinin have been reported[6] and because the structural difference is very small: In peridinin a stereochemically more complex allenol moiety C5(−OH)−C6=C7=C8 replaces for the enyne moiety C5=C6−C7≡C8 of pyrrhoxanthin. Nonetheless, we consider pyrrhoxanthin to be a more demanding target molecule for total synthesis than peridinin as observations made in the literature[1b,7] and by ourselves indicate that establishing and conserving an *E* configuration of the C9=C10 bond in C7≡C8-containing precursors of pyrrhoxanthin (**5**) and in pyrrhoxanthin itself present a significant challenge.

Completely synthetic pyrrhoxanthin (**5**; Scheme 1) has been obtained only once previously—by Ito et al.: as a 25% constituent of a 1:1 mixture of the racemic diastereomers **3** and **4** (Scheme 1).[8] The key and simultaneously terminating step of their approach was initiated by the addition of lithio-*rac*-**1** to the aldehyde ester *rac*-**2**. However, after preparative HPLC and preparative TLC, **3** and **4** were obtained in only 3.7% yield (not overall yield!). A much more efficient synthetic strategy was used by de Lera et al.[7] They started from the bromoiodobutenolide **8**, which our group had synthesized previously,[9] and utilized the possibility to[10] functionalize it stepwise by Stille couplings following the order indicated by the labels ① and ②. Yet in the end, this approach led to (9*Z*)-pyrrhoxanthin (**6**), which could not be isomerized to give naturally configured pyrrhoxanthin (**5**).[11]



Scheme 1. Natural pyrrhoxanthin (**5**), unnatural pyrrhoxanthins (**3**, **4**, **6**), and successfully strategies for the total synthesis of the latter.[7,8]

We now describe the first total synthesis of naturally configured pyrrhoxanthin (**5**), which is based on the following retrosynthetic analysis (Scheme 2, upper part):

1) Four building blocks (**10**, **12**, **13**, **14**) are combined in the last stages of this synthesis, which makes it highly convergent.
2) The identity of these four building blocks followed in part from our intention to construct pyrrhoxanthin (**5**) "from right to left". When this sense of assembly is followed, the *E*-configured C9=C10 bond is exposed only in the final product **5** to the presence of the C7≡C8 bond, which we deemed most prone to facilitate $E \rightarrow Z$ isomerization.
3) Two of our key building blocks possess a reactive moiety "in duplicate". The hitherto unknown heptatrienyldistan-

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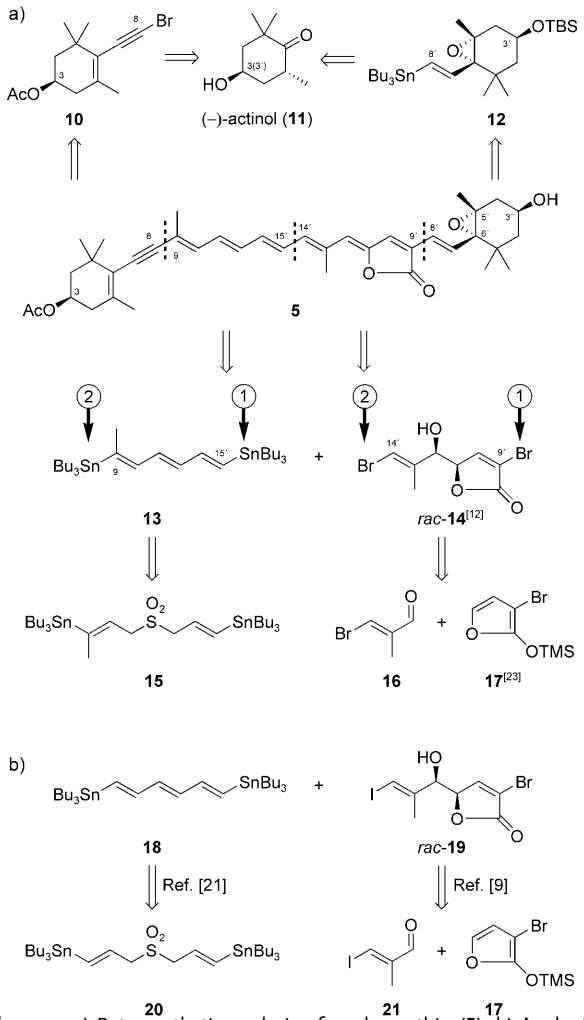


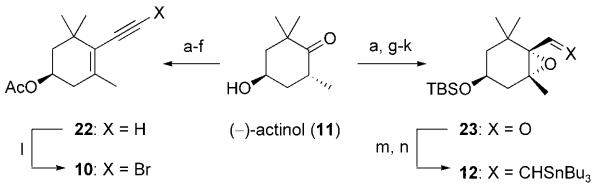
Scheme 2. a) Retrosynthetic analysis of pyrrhoxanthin (**5**). b) Analogies from the literature concerning the projected generation of the bifunctional building blocks **13** and *rac*-**14** (bottom): retrosyntheses of hexatrienyldistannane **18** from sulfone **20**, and of "bromoiododiolefin" *rac*-**19** from siloxyfuran **17** and iodomethacrolein **21**. TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl.

nane **13** contains two units with the structural motif C=C–$SnBu_3$, and the novel dibromobutenolide *rac*-**14**[12] has two C=C–Br groups. In each building block, one of the reactive groups was intended to participate in a Stille coupling[13] and the remaining reactive group was intended for a different Stille coupling. The strategy for the linkage of the building blocks, "from right to left" (vide supra), was expected to fit the order of reactivity in heptatrienyldistannane **13**, which is determined by sterics, and that in the dibromobutenolide *rac*-**14**, which is governed by electronics.[14]

4) Whereas the "right-hand" six-membered-ring reagent **12** is known,[6f,g,7,15,17] bromoalkyne **10**, which serves as the "left-hand" six-membered-ring reagent, was prepared for the first time in the course of the present study. This bromoalkyne was required because in model reactions the analogous iodoalkyne[18] underwent Stille coupling with alkenyl(tributylstannanes) only to some extent, and an I/$SnBu_3$ exchange reaction competes or even predominated.[19]

The retrosynthetic disconnections of Scheme 2a trace both the new six-membered ring **10** and the known six-membered ring **12** back to (−)-actinol (**11**). The latter is an established starting material for the synthesis of carotenoids with an oxygenated six-membered ring.[2] We intended to prepare the heptatrienyldistannane **13** via the sulfone **15** by a Ramberg–Bäcklund reaction,[20] in the same manner that had proved successful for obtaining the hexatrienyldistannane **18** via the sulfone **20**.[21] The "dibromodiolefin" *rac*-**14** was conceived to result from a *syn*-selective vinylogous Mukaiyama aldol addition[22] of siloxyfuran **17**[23] to bromomethacrolein (**16**) in exactly the same way by which we had transformed iodomethacrolein (**21**) into the "bromoiododiolefin" *rac*-**19** en route to the bromoiodobutenolide **8**.[9]

The synthesis of the bromoalkyne **10** (Scheme 3) began with steps from the literature: *tert*-butyldimethylsilylation[24] of (−)-actinol (**11**), addition of lithio(trimethylsilyl)acetylide,[24] and desilylation of the C≡C bond with potassium methoxide.[24b,25] Thereafter we followed Schmidt-Leithoff's[25] permutation of reaction conditions, which had been applied previously only to related molecules: dehydration of the alkynol with $CuSO_4$ in refuxing xylene[26] to give the enyne and exchange of the TBSO protecting group for an AcO group. Under $AgNO_3$ catalysis[27] the terminally unfunctionalized alkyne **22**[26] and NBS provided the desired bromoalkyne **10** in 41% overall yield for the seven steps from **11**. Our



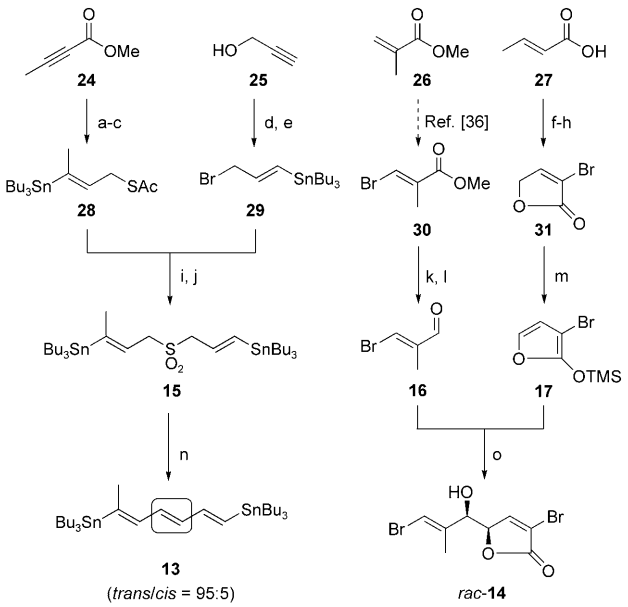
Scheme 3. Syntheses of the six-membered-ring reagents **10** and **12**. a) TBSCl (1.07 equiv), NEt_3 (1.1 equiv), DMAP (1.05 equiv), CH_2Cl_2, 0°C, 17 h; 90% (Ref. [6f]: 97%); b) LiC≡CTMS (1.05 equiv), THF, 0°C, 3 h; c) K_2CO_3 (1.5 equiv), MeOH, 25°C (Ref. [25]: 100% over 2 steps); d) $CuSO_4 \cdot 4H_2O$, xylene, Dean–Stark trap, 50 h; 67% over 3 steps (Ref. [25]: 93%); e) $Bu_4N^+F^-$ (3.0 equiv), THF, 25°C, 12 h; 84% (Ref. [25]: 86%); f) Ac_2O (3 equiv), DMAP (0.1 equiv), pyridine, 25°C; 88% (Ref. [25]: 89%); g) LDA (1.60 equiv), addition of the TBS ether obtained in step (a), −78°C, 1 h; addition of $PhN(SO_2CF_3)_2$ (1.5 equiv), THF, 25°C, 2 d; 84% (Ref. [8b]: 89%); h) Stream of CO, MeOH (30 equiv), NEt_3 (3 equiv), $[Pd(PPh_3)_4]$ (3 mol%), DMF, 80°C, 24 h; 92% (Ref. [6f]: 99%); i) DIBAH (2.5 equiv), CH_2Cl_2, −78°C, 25 min; 84% (with $LiAlH_4$:[6e] 87%); j) *t*BuOOH (2 equiv), D-(−)-DIPT (2.3 equiv), $Ti(OiPr)_4$ (1.5 equiv), MS (4 Å), CH_2Cl_2, −30°C, 1.5 h; 95%, >98% *de* (Ref. [6f]: 95%, 98% *de*); k) Dess–Martin periodinane, CH_2Cl_2, 25°C, 2.5 h; 85% (Ref. [6f]: 92%); l) NBS (1.3 equiv), $AgNO_3$ (10 mol%), acetone, 25°C; 92%; m) $Me_3SiCH{=}N{=}N$ (1.2 equiv), LDA (1.1 equiv), THF, −30°C, 15 min; addition of the aldehyde **23** (1.0 equiv) obtained in step (k), 1 h (Ref. [15]: 92%); n) Bu_3SnH (3 equiv), $[Pd(PPh_3)_4]$ (5 mol%), BHT (5 mol%), THF, 0°C, 90 min; 72% yield of the *trans*-alkenylstannane over 2 steps (Ref. [6f]: 53% over 2 steps); BHT = 2,6-di-*tert*-butyl-4-methylphenol; DIBAH = diisobutylaluminum hydride; D-(−)-DIPT = D-(−)-diisopropyl tartrate; DMAP = 4-(dimethylamino)pyridine; LDA = lithium diisopropylamide; MS = molecular sieves; NBS = *N*-bromosuccinimide.

preparation of the *trans*-alkenylstannane **12** (Scheme 3) from (−)-actinol (**11**) followed established procedures.[6d–f,8b,15] Usually our yields were slightly below the published values. However, the C_1 homologation giving the alkyne (step m) by Shioiri's method and the Pd-catalyzed hydrostannylation of this alkyne (step n) succeeded in 72% yield rather than in the 53% reported earlier.[6f] All in all, the stannane **12** was available in 34% overall yield by this eight-step synthesis.

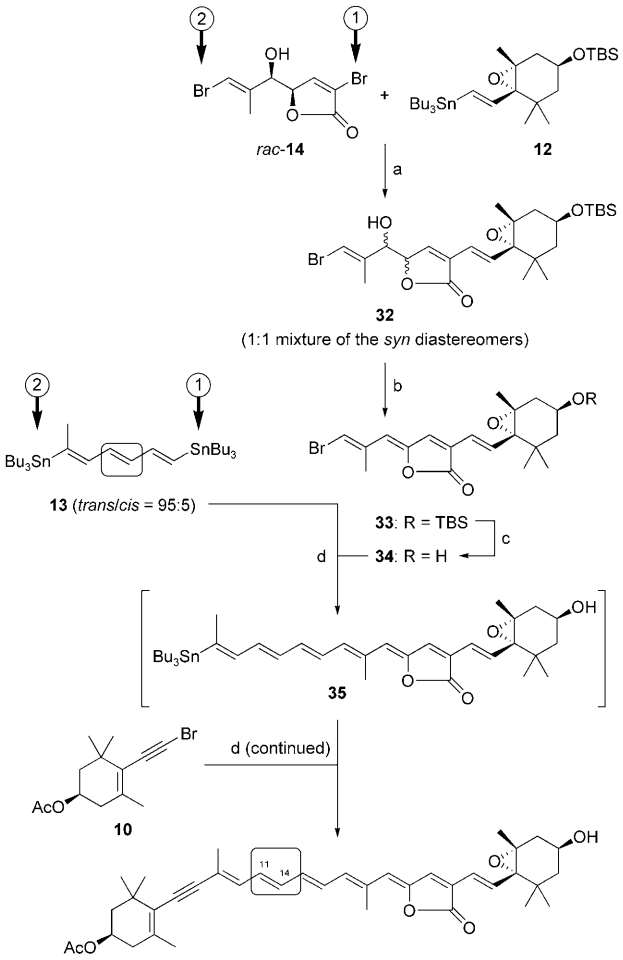
The synthesis of the heptatrienyldistannane **13** by a Ramberg–Bäcklund reaction[20] of the sulfone **15** was realized (Scheme 4) in accordance with our retrosynthetic analysis in Scheme 2. In the first step, the tetrolic ester **24** and $(Bu_3Sn)BuCu(CN)Li_2$[28] underwent the same kind of *cis*-hydrostannylation[29] that had been described by Parrain et al. for tetrolic acid.[30] Reduction of the resulting unsaturated ester with DIBAH furnished an allylic alcohol in 99% yield. Under Mitsunobu conditions this was converted into the thioacetate **28** (85% yield). Next, propargyl alcohol (**25**) was *cis*-hydrostannylated[31] using $(Bu_3Sn)BuCu(CN)Li_2$.[28] The resulting (tributylstannyl)allyl alcohol (84% yield) was converted into the known[32] allyl bromide **29** in 88% yield by treatment with CBr_4 and PPh_3. Dissolving KOH pellets and adding allyl bromide **29** to a solution of the thioacetate **28** in methanol brought about a tandem reaction ("sequential transformation")[33] consisting of a transesterification and an S_N2 alkylation to delivered an unsymmetric sulfide in 87% yield. The latter was oxidized with H_2O_2 and cat. $(NH_4)_6Mo_7O_{24}$[21] to give a 71% yield of the sulfone **15**. When we treated this compound with CBr_2F_2 and KOH on Al_2O_3 in CH_2Cl_2—well-established conditions for Ramberg–Bäcklund syntheses of many conjugated trienes[34]—the heptatrienyldistannane **13** was formed as a 95:5 *trans*/*cis* mixture (78% yield). In addition, an isomeric mixture of heptatrienylmonostannanes was formed in 4% yield and could not be separated by flash chromatography on silica gel.[35] Most likely these monostannanes originated from the distannane **13** by protonolysis of the sterically less hindered C–$SnBu_3$ bond. The overall yield of the heptatrienyldistannane **13** from the tetrolic ester **24** was 33%.

The "dibromodiolefin" *rac*-**14** was prepared from bromomethacrylate **30**[36] and crotonic acid (**27**) (Scheme 4). Ester **30** was reduced with $LiAlH_4$[37] and the resulting alcohol reoxidized with MnO_2 to obtain enal **16**.[38] A Wohl–Ziegler bromination of crotonic acid (**27**) and the addition of bromine to the C=C bond yielded 1,2,3-tribromobutyric acid. This compound lactonized in boiling water, whereupon a β elimination furnished the bromobutenolide **31**. The trimethylsiloxyfuran **17** derived therefrom[23] and enal **16** were treated with slightly more than 1.0 equiv of $BF_3{\cdot}OEt_2$; as expected,[22] a highly diastereoselective vinylogous Mukaiyama aldol addition ensued. It gave a 95:5 *syn*/*anti* mixture of products initially, from which we separated the major addition product *rac*-**14** by flash chromatography on silica gel[35] in 52% yield (over two steps).

Scheme 5 shows the final steps of our total synthesis of naturally configured pyrrhoxanthin (**5**). One of the prerequisites of our overall linkage strategy "from right to left" materialized in the inaugural step, which was a Stille coupling between the "dibromodiolefin" *rac*-**14** and the six-membered-ring building block **12**. Under the combined influence of $[Pd(PPh_3)_4]$ and CuI[39] the reactivity order of the termini of compound *rac*-**14** was exactly as desired: the observed exclusive monocoupling of the right-hand moiety rendered the coupling product **32**, which was obtained as a 1:1 mixture of the two *syn* diastereomers in 75% yield. The ensuing dehydration delivering the alkylidene butenolide **33** had to be *anti* selective for the resulting C=C bond to be uniquely *Z* configured. This was possible by addition of thiocarbonyldiimidazole in analogy to the procedure described recently for an analogous dehydration.[17] However, the reaction got stuck after the initial O functionalization had occurred. In contrast to the preceding case[17] the *anti* elimination followed



Scheme 4. Syntheses of the bifunctional building blocks **13** and **14**. a) CuCN (1.3 equiv), *n*BuLi (2.6 equiv), THF, −78°C, →25°C, → −78°C, $HSnBu_3$ (2.6 equiv), MeOH (1.5 equiv), **24**, 1 h; 82% (Ref. [29]: 100%); b) DIBAH (2.3 equiv), CH_2Cl_2, −78°C, 2 h; 99% (Ref. [25]: 92%); c) DIAD (1.5 equiv), PPh_3 (1.5 equiv), AcSH (1.5 equiv), THF, 0°C, 12 h; 85%; d) CuCN (1.2 equiv), *n*BuLi (2.4 equiv), THF, −78°C, for a short time →25°C, −78°C, $HSnBu_3$ (2.4 equiv), −30°C, 12 h; 84% (Ref. [31]: 66%); e) CBr_4 (1.2 equiv), PPh_3 (1.2 equiv), CH_2Cl_2, 0°C, 3.5 h; 88% (Ref. [21]: 82%); f) NBS (1.0 equiv), AIBN (cat.), CCl_4, 60°C; 4.5 h; g) Br_2 (1.2 equiv), CCl_4, 40°C, 6 h (Ref. [9]: 87% over 2 steps); h) H_2O, 100°C, 2 h; 11% over 3 steps; i) **28** (1.05 equiv), KOH (5 equiv), MeOH, 0°C, 5 min; **29**, 1 h; 87%; j) H_2O_2 (5 equiv), $(NH_4)_6Mo_7O_{24}$ (0.2 equiv), EtOH, 0°C, 1 h; 71%; k) $LiAlH_4$ (1.0 equiv), Et_2O, 0°C, addition of **30**, →25°C, 3 h; 94% (Ref. [37]: 95–100%); l) MnO_2 (20.0 equiv), CH_2Cl_2, 25°C, 24 h; 83% (Ref. [38]: 92–94%); m) Me_3SiCl (1.1 equiv), NEt_3 (1.2 equiv), Et_2O, 0°C, 12 h; 75% (Ref. [23b]: 44%; Ref. [23c]: 78%); n) CBr_2F_2 (4 equiv), KOH (10 equiv) on Al_2O_3 (1:2), CH_2Cl_2, 0°C, 15 min, 25°C, 30 min; 82% yield of a 95:5 mixture of **13** (78%; *trans*,*trans*,*E*/*trans*,*cis*,*E* = 95:5) and 6-(tributylstannyl)hepta-1,3,5-triene (4%; *trans*,*E*/*trans*,*Z* = 67:33); o) **16** (1.1 equiv), $BF_3{\cdot}OEt_2$ (1.1 equiv), CH_2Cl_2, −78°C, 5 h; over the 2 steps from **31**: 52% diastereomerically pure *rac*-**14** [separated from an initial 95:5 *syn*/*anti* mixture; Ref. [12]: 72% diastereomerically pure *rac*-**14** (separated from an initial 90:10 *syn*/*anti* mixture)]. AIBN = 2,2′-azobis(isobutyronitrile); DIAD = diisopropyl azodicarboxylate; DIBAH = diisobutylaluminum hydride; NBS = *N*-bromosuccinimide.



Compound	A[a] + 5 + 11-*cis*-5 + B + C					Yield 5 [%] after HPLC
Retention time[b] [min]	27.8	29.8	32.4	33.9	34.9	
Relative yield[c] [%]	3 :	80 :	13 :	1 :	3	38

Scheme 5. Total synthesis of pyrrhoxanthin (**5**). a) **12**, *rac*-**14** (1.16 equiv), $[Pd(PPh_3)_4]$ (10 mol%), CuI (1.77 equiv), NMP, 50°C, 12 h; 75%; b) Thiocarbonyldiimidazole (2 equiv), CH_2Cl_2, 0°C, 1 h; NEt_3 (5 equiv), 5 min; 73% isomerically pure **33** (separated from a 91:9 *Z*/*E* mixture); c) aq. HCl (1 M)/MeOH/THF (1:1:4), 0°C, 1.5 h; 94%; d) **34**, **13** (2.0 equiv), $Bu_4N^+Ph_2PO_2^-$ (4 equiv), $[Pd_2(dba_3)\cdot CHCl_3]$ (5 mol%), P(2-furyl)$_3$ (0.25 equiv), BHT (250 ppm), exclusion of light, NMP, 25°C, 2 h; **10** (3 equiv), 55°C, 3 h; flash chromatography gave **5** in a mixture with side products; preparative HPLC gave pure **5** in 38% yield. BHT = 2,6-di-*tert*-butyl-4-methylphenol; dba = *trans*,*trans*-dibenzylidene acetone; NMP = *N*-methylpyrrolidone.
Table footnotes: [a] Compound **A** is either 15-*cis*-pyrrhoxanthin or 11-*cis*,15-*cis*-pyrrhoxanthin; the side products **B** and **C** could not be characterized because of their low yield and their lability, respectively. [b] HPLC separation: LiChrospher column (4×250 mm, E. Merck), 100 RP-18-endcapped, 5 μm, CH_3CN/H_2O (80:20), eluent flow 1.0 mL min^{-1}, 25°C. [c] Set equal to the relative areas of the absorption peaks that the UV detector of the HPLC instrument recorded for the eluate at $\lambda = 400$ nm.

only after the addition of triethylamine—but then within a few seconds. A 91:9 *Z*/*E* mixture of the alkylidenebutenolides formed, from which we isolated the *Z* isomer **33** by flash chromatography on silica gel[35] in 73% yield. Compound **33** was desilylated by treatment with hydrochloric acid without isomerization to provide the bromobutenolide **34** in 94% yield.

Attempted Stille couplings between the iodoalkyne analogue[18] of bromoalkyne **10** and alkenyl(tributylstannanes), which we had employed as models of the pyrrhoxanthin precursor **35**, had been unsuccessful.[19] As we had observed that an I/$SnBu_3$ exchange reaction occurs between the iodoalkyne and the model stannanes, we prepared the previously unknown bromoalkyne **10**. The latter proved capable of undergoing Stille couplings, particularly in the presence of $[Pd_2(dba)_3\cdot CHCl_3]$, the sterically undemanding ligand P(2-furyl), and the Bu_3Sn trap $Bu_4N^+Ph_2PO_2^-$.[40] In this manner we coupled the heptatrienyldistannane **13** with the bromobutenolide **34** in the terminating step exclusively at the sterically less hindered C_{sp^2}–$SnBu_3$ terminus and obtained the pyrrhoxanthin precursor **35** (Scheme 5). Owing to the tremendous lability of this compound, we prepared it in brown glass vessels, used O_2-free, N_2-saturated NMP as the solvent, added 2,6-di-*tert*-butyl-4-methylphenol as a radical scavenger, and subjected it to the final coupling with 3 equiv of the bromoalkyne **10** without prior workup. This reaction and the subsequent workup were conducted following the same precautionary measures. Prepurification by flash chromatography on silica gel[35] delivered a mixture, which consisted—according to analytical reversed-phase HPLC—of pyrrhoxanthin (**5**) (80%) along with probably 13, 3, 3, and 1% of at least four isomers. Purification of this mixture by preparative reversed-phase HPLC furnished isomerically pure pyrrhoxanthin (**5**) in 38% yield.

The ^{1}H NMR (499.7 MHz) spectrum of our synthetic pyrrhoxanthin (**5**) in C_6D_6, its ^{13}C NMR (125.7 MHz) spectrum, the H,H- and C,H-COSY spectra and the NOE cross-peaks in the ROESY spectrum allowed us to assign all ^{1}H NMR resonances and to determine the configuration of each C=C bond.[41] Similarly, we determined all C=C bond configurations in the major side product of **5**, the pyrrhoxanthin isomer 11-*cis*-**5**, which was observed for the first time.

The success of this first stereoselective total synthesis of enantiomerically pure pyrrhoxanthin (**5**) is due to its high convergency and to the fact that the very isomerization-prone *E*-configured C=C bond of the enyne moiety C7≡C8-C9=C10 was established only in the very last step. Our synthetic strategy traced the target molecule back to four building blocks (**10**, **12**, **13**, and *rac*-**14**) designed to be combined by Stille couplings. Being monofunctional coupling partners, the six-membered-ring building blocks **10** and **12** served to introduce the extremities of the target structure. In contrast, the heptatrienyldistannane **13** and the dibromobutenolide *rac*-**14** are bifunctional Stille substrates, which were used as linking reagents and coupled step by step with rigorous regiocontrol. These building blocks contributed the center part to the pyrrhoxanthin molecule.

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