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Total synthesis of (8*R*,6′*R*)-peridinin-5,8-furanoxide†

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The first total synthesis of (8*R*,6′*R*)-peridinin-5,8-furanoxide, a C_{37} xanthophyll norcarotenoid, has been achieved. The key steps of the synthetic sequence are a Julia–Kocienski condensation and a late stage stereoretentive Stille cross-coupling of an iodoallene.

Among the diverse functions of carotenoids in Nature, their role in photosynthesis as light-harvesting antennae and in photoprotection by deactivating $^1O_2$* and ^{3}Chl* and reducing the formation of reactive oxygen species (ROS) by non-photochemical fluorescence quenching (NPQ) mechanisms is the most important for the producing organisms.[1,2]

The xanthophyll peridinin **1** (ref. 3) (Fig. 1) is one of the most abundant photosynthetic pigments in microalgae. Two norcarotenoids (C_{37}) related to **1**, identified as the diastereoisomers at C8 of peridinin-5,8-furanoxide **2**, have been isolated from a dinoflagellate of the genus *Symbiodinium*, which is a symbiont of the host soft coral *Clavularia viridis*, a rich source of prostaglandins.[4]

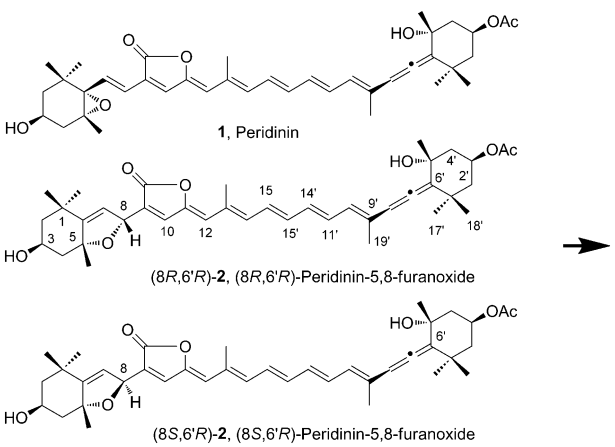

Fig. 1 Allene-containing xanthophylls.

Although the treatment of peridinin with acid generates a mixture of 5,8-furanoxide derivatives by rearrangement of the butadiene oxide subunit,[5] carefully controlled experiments carried out by subjecting peridinin to the isolation conditions and purification protocols did not reveal the presence of these derivatives. Therefore, the peridinin-5,8-furanoxides appear to be true natural products and not artifacts.[4] A few other C_{40} carotenoid furanoxides are known.[6] As a continuation of our studies on the total synthesis of carotenoids,[7] we targeted the peridinin-5,8-furanoxides. We were prompted not only by the synthetic challenges inherent in their structures (non-symmetric C_{37} norcarotenoids with five stereogenic centers, one stereogenic axis and a butenolide as part of the conjugated polyene chain) but also because of the potent growth-inhibitory activity of unprecedented profiles that these compounds exhibited against a panel of human cancer cells.[4]

In a departure from our approach to peridinin **1**,[7d] we dissected compound **2** into three fragments (Scheme 1). The bis-functionalized C_6 central component **4** featuring a terminal stannane and an allyl-benzothiazolyl (BT)-sulfone was traced back to but-2-yn-1-ol **7**. Connective Stille and Julia–Kocienski reactions involving **4** were conceived to attach the cyclic end group partners of complementary reactivity, namely **5** (a C_{11} fragment) and **3** (a C_{20} fragment), which are functionalized with allenyliodide and aldehyde groups, respectively.

We considered it to be feasible that 2,5-dihydrofuran **3** could be obtained from the acid-catalyzed rearrangement of epoxide **6**, which is precedented for carotenoids.[5,8] Compound **6** would be obtained by the Stille cross-coupling of alkenylstannane **10** and 2-bromoalkylidenebutenolide **9**. The construction of the alkylidenebutyrolactone **9** would be based on the metal-mediated cyclization of the dienynoic acid obtained by Sonogashira coupling of ethyl (*E*)-dibromoacrylate **12** and protected enynol **11** followed by saponification. Iodoallene **5**, derived from (−)-actinol **8**, was proposed as the electrophilic component for the Stille coupling with stannanes in a reaction that would proceed with retention of configuration, as confirmed in previous studies with model systems.[9,10]

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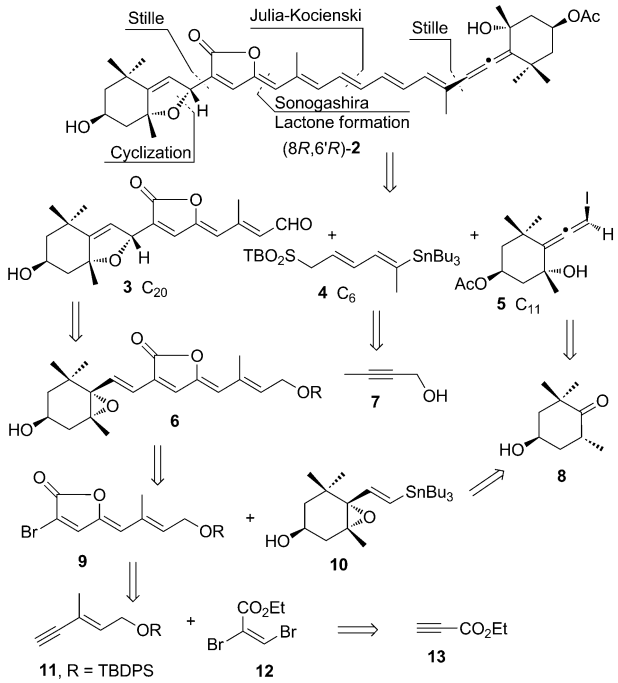
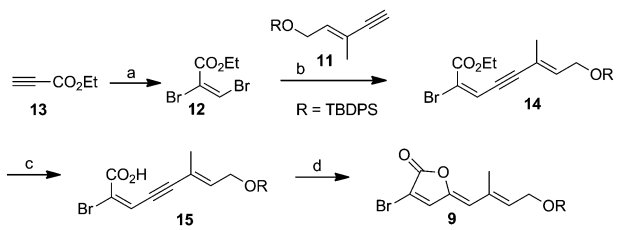


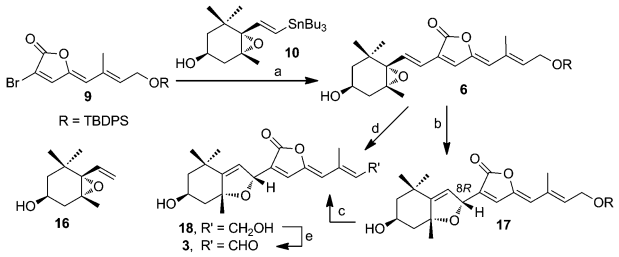
Scheme 1 Retrosynthetic analysis.

Treatment of ethyl propiolate **13** with pyridinium tribromide in CH_2Cl_2 at ambient temperature[11] produced dibromide **12** in 75% yield. Sonogashira coupling of **12** with the TBDPS-protected enynol **11** using $PdCl_2(PPh_3)_2$ and CuI in THF–Et_3N (4 : 1) at 25 °C afforded dienyne **14** in 75% yield (together with small amounts of the homodimer and the bis-coupled derivative, ESI†). Under the conditions reported by Negishi (20 mol% Ag_2CO_3 in DMF, 25 °C)[12] the silver carbonate-mediated cyclization of dienynoic acid **15**, obtained by mild saponification of ester **14** ($LiOH{\cdot}H_2O$, THF/H_2O, 25 °C), provided **9**[13] in 75% yield (Scheme 2).

The Stille coupling of **9** and previously described stannane **10**[7d,14] under Fürstner conditions[15] at 0 °C led to **6** in 84% yield together with small amounts of destannylated product **16**. The known rearrangement of butadiene oxide to 2,5-dihydrofuran units of carotenoids[5] was attempted next using **6**. The rearrangement of **6** induced by TFA provided 2,5-dihydrofuran **17** with *R* configuration (H8 resonance at δ = 5.60 ppm; *cf.* δ = 5.50 ppm for the *S* epimer in the ^{1}H-NMR spectra; see ESI† for the comparison of the ^{1}H-NMR data of synthetic and natural compound **2**) in 46% yield. Deprotection of the silyl ether with the HF–Py complex in THF[16] delivered allylic alcohol **18** in 52% yield. More conveniently,



Scheme 2 *Reagents and conditions*: (a) $C_5H_5NH^+Br_3^-$, CH_2Cl_2, 25 °C, 15 h, 75%. (b) $PdCl_2(PPh_3)_2$, CuI, THF–Et_3N (4 : 1), 25 °C, 4 h, 87%. (c) $LiOH{\cdot}H_2O$, THF–H_2O, 25 °C, 6 h. (d) Ag_2CO_3, THF, 25 °C, 6 h, 75% two steps.

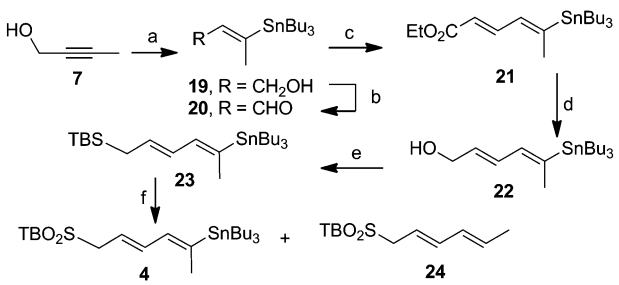


Scheme 3 *Reagents and conditions*: (a) CuTC (1.5 equiv.), $[NBu_4][Ph_2PO_2]$ (1.25 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), DMF, 0 °C, 3.5 h, 84% (**16**, 4.5%). (b) TFA (0.35 equiv.), CH_2Cl_2, 0 to 25 °C, 5 h, 46%. (c) HF–Py, THF, Py, 25 °C, 52%, 20 h. (d) 30% H_2SO_4, CH_3CN, −10 °C, 15 h, 41%. (e) MnO_2, Na_2CO_3, CH_2Cl_2, 0 °C, 1 h, 88%.

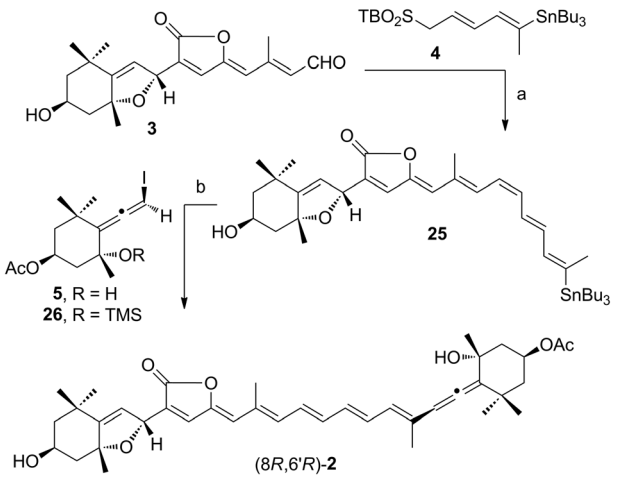
the rearrangement and deprotection could be effected concomitantly upon treatment of **6** with 30% H_2SO_4 in CH_3CN (41% yield), which provided (8*R*)-**18** admixed with minor amounts of diastereomers (8*S*)-**18** and (13*Z*,8*R*)-**18** in a 91 : 3 : 6 ratio. Oxidation of (8*R*)-**18** with MnO_2 and Na_2CO_3 in CH_2Cl_2 at 0 °C furnished aldehyde **3** in 88% yield (Scheme 3).

The synthesis of the C_6 central fragment started with the stannylcupration/protonolysis of but-2-yn-1-ol **7**,[17] which was followed by oxidation of **19** and HWE condensation of **20** with triethyl phosphonoacetate.[18] Ester **21**, obtained in 94% yield, was quantitatively reduced with DIBAL-H to stannyldienol **22**, and this alcohol was employed in the Mitsunobu reaction with benzothiazolylthiol to produce sulfide **23**. Oxidation of **23** with H_2O_2 and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ at 0 °C[19] furnished allyl-BT-sulfone **4** in 75% yield and **24** in 8% yield (Scheme 4).

As discovered during the synthesis of peridinin **1**,[7b,d] the Julia–Kocienski reaction was more conveniently performed in advance of the Stille cross-coupling, since the *Z* selectivity of the former condensation between unsaturated partners (aldehydes and BT-sulfones)[20] could be "corrected" by the reaction conditions of the Pd-catalyzed coupling.[7d] Julia–Kocienski condensation of **3** and **4** afforded a 10 : 1 mixture of *Z*/*E* isomers at the newly formed double bond in 74% yield (Scheme 5). The final Stille coupling of stannane **3** and iodoallene **5** under stereoretentive conditions [$Pd(PPh_3)_4$, DMF, 40 °C][9] led, to our surprise, to a mixture of stereoisomers at the allene axis, as shown by the presence of allene H signals for both epimers at δ = 6.05 ppm (*R*) and δ = 6.16 ppm (*S*) in the ^{1}H-NMR spectra. Our experimental and



Scheme 4 *Reagents and conditions*: (a) *n*-BuLi, $(Bu_3Sn)_2$, CuCN, THF–MeOH, −10 °C, 15 h, 99%. (b) MnO_2, CH_2Cl_2, 25 °C, 3.5 h, 92%. (c) *n*-BuLi, THF, triethyl phosphonoacetate, 25 °C, 2 h, 94%. (d) DIBAL–H, THF, −78 °C, 1 h, 99%. (e) BTSH, DIAD, THF, 0 °C, 0.5 h, 86%. (f) 35% H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, 0 °C, 15 h, 75% (**24**, 8%).



Scheme 5 *Reagents and conditions*: (a) NaHMDS, THF, −78 °C, 2 h, 74% (10 : 1 *Z*/*E* ratio). (b) (i) $Pd(PPh_3)_4$, DMF, 40 °C, 18 h. (ii) TBAF, THF, 0 °C, 1 h, 55%.

computational insight into this coupling[9] suggested that the inversion product arises from the S_N2' substitution of I by Pd(0) at the allene unit and metallotropy of the organopalladium intermediate, and that this pathway should be prevented using TMS-protected iodoallenol **26**.[9] In the event, the coupling of **25** and **26** under the same conditions followed by removal of the silyl ether (TBAF, THF) led to (8*R*,6′*R*)-**2** in 55% yield.

In summary, we have achieved the first total synthesis of the xanthophyll (8*R*,6′*R*)-peridinin-5,8-furanoxide in a sequence that entails the late stage stereoretentive Stille cross-coupling of an allenyliodide[9,10] and a stannane, which occurs with concomitant C15═C15′ double bond isomerization. The required stannane was prepared by Julia–Kocienski condensation of **3** and the central conjunctive reagent **4**. The preparation of the 2,5-dihydrofuran ring was based on the acid-catalyzed rearrangement of the butadiene oxide functionality with the alkylidene butyrolactone substructure in place. (8*R*,6′*R*)-**2** and (8*S*,6′*R*)-**2** are the only C_{37} norcarotenoid furanoxides of the two dozen congeners reported to date.[6] These C_{40} furanoxides have been obtained (with the exception of the aurochrome diastereomers)[21] by partial synthesis from the corresponding putative biogenetic precursor carotenoids with butadiene epoxide structural units.

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