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Synthesis of Symmetrical Carotenoids by a Two-Fold Stille Reaction

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Received March 18, 2002

Abstract: β-Carotene **1** and (3*R*,3′*R*)-zeaxanthin **2** have been stereoselectively prepared in a highly convergent fashion by a 2-fold Stille cross-coupling reaction. The C_{12}-pentaenylbis-stannane **8** is the central "lynchpin" that connects two units of the terminal C_{14}-iodides **9** and **17** to afford **1** and **2**, respectively.

Carotenoids[1] are highly conjugated polyenes that play fundamental roles as photoprotective and antioxidation agents and are dietary sources of vitamin A and other naturally ocurring retinoids.[2,3]

The carotenoid polyenic chain has traditionally been synthesized by consecutive or convergent double bond forming strategies, commonly a Wittig reaction (or some of its variants) or a Julia-type olefination.[1c] These procedures generally afford mixtures of *E*/*Z* geometric isomers which are very difficult to separate.

The alternative strategy featuring generation of single bonds connecting Csp^2 atoms has somehow been neglected for this particular class of conjugated polyenes. Recently, however, Negishi and Zeng reported a stereoselective and highly efficient synthesis of carotenoids using a Pd- and Zn-catalyzed cross-coupling of alkenyl fragments. The nucleophile was generated by Al−Zn transmetalation following zirconium-mediated methylalumination of alkynes.[4] Using two C_5 and one C_2 halides as electrophiles, these C_{40} polyolefins were built by an iterative sequence which displays a $C_{14} + C_5 + C_2 + C_5 + C_{14}$ pattern.[5]

We wish to report another stereocontrolled approach to symmetrical carotenoids based on a convergent $C_{14} + C_{12} + C_{14}$ building principle, featuring a 2-fold Stille cross-coupling of C_{12}-bis-stannane **8** and C_{14}-alkenyl iodides **9** and **17**, yielding β-carotene **1** and (3*R*,3′*R*)-zeaxanthin **2**, respectively.

Pentaenylbis-stannane **8** was prepared by the modified one-pot Julia olefination[6] that condensates two C_6 fragments, both derived from known stannyldienol **3**.[7] The synthesis of the required C_6-sulfone **6** started with the treatment of **3** with 2-mercaptobenzothiazole under Mitsunobu conditions to afford benzothiazolyl sulfide **5** (96% yield). Oxidation of the sulfide to the sulfone was troublesome, and under the best conditions [$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, 35% H_2O_2, EtOH, 25 °C][6] afforded **6** in moderate yields (61%) together with **7** (31%), the protiodestannylation product.[8,9]

Generation of the anion of sulfone **6** with NaHMDS at −78 °C, followed by addition of **4**,[7a] afforded with high stereoselectivity in 83% yield symmetrical *all-E*-pentaene **8**,[10] the longest substituted conjugated bis-stannane yet reported.

The trisubstituted alkenyl iodides **9**[11a] and **17** were in turn prepared by Negishi's methodology,[11] using the zirconium-assisted methylalumination−iodination of the precursor alkynes. The synthesis of dienyne **15** started with the protection of enantiopure (*R*)-**10** to **11**[12a] followed

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(1) For recent monographs, see (a) Britton, G.; Liaaen-Jensen, S.; Pfander, H., Eds. *Carotenoids. Part 1A. Isolation and Analysis*; Birkhäuser: Basel, 1995. (b) Britton, G.; Liaaen-Jensen, S.; Pfander, H., Eds. *Carotenoids. Part 1B. Spectroscopy*; Birkhäuser: Basel, 1995. (c) Britton, G.; Liaaen-Jensen, S.; Pfander, H., Eds. *Carotenoids. Part 2. Synthesis*; Birkhäuser: Basel, 1996.

(2) β-Carotene dioxygenases, enzymes that effect the centric cleavage of β-carotene to retinal, have been characterized; see (a) Wyss, A.; Wirtz, G.; Woggon, W.-D.; Brugger, R.; Wyss, M.; Friedlein, A.; Bachmann, H.; Hunziker, W. *Biochem. Biophys. Res. Commun.* **2000**, *271*, 334. (b) von Linting, J.; Vogt, K. *J. Biol. Chem.* **2000**, *275*, 11915. For a mechanistic proposal of the enzymatic reaction, see Leuenberger, M. G.; Engeloch-Jarret, C.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2614.

(3) Vision is also believed to be affected by the intake of certain hydroxylated carotenoids, such as zeaxanthin **2**. Their suggested role as optical filters and antioxidation agents is considered to help decrease the risk of developing AMD (age-related macular degeneration), the leading cause of blindness in elderly people; see Rando, R. R. *Chem. Biol.* **1996**, 3, 255.

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(8) Other experimental conditions proved unsuccessful. The use of MCPBA in the presence of Na_2CO_3 or Et_3N led to a mixture of products. On the other hand, cat. TPAP/NMO in CH_3CN (Guerlin, K. R.; Kende, A. S. *Tetrahedron Lett.* **1993**, *34*, 5369) returned unreacted starting material. The use of Oxone (Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287) in MeOH/H_2O led to even greater amounts of **7**. In addition, no improvement was observed when the Mo(VI)-based oxidant was slowly added to the solution of the sulfide in MeOH/H_2O or when base was added to neutralize the reaction medium.

(9) Sulfone **7** was obtained as an unseparable (HPLC) mixture of *E*/*Z* isomers. Although we have not carried out detailed mechanistic studies, the isolation of double bond isomers of **7** suggest the intervention of a reversible allyl sulfoxide−allyl sulfenate rearrangement following the initial oxidation of sulfide **5**.

(10) For the use of other symmetrical bis-stannanes in organic synthesis, see (a) (*E*,*E*)-1,4-bis(trimethylstannylbutadiene: Kiehl, A.; Eberhardt, A.; Adams, M.; Enkelmann, V.; Müllen, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1588. Kiehl, A.; Eberhardt, A.; Müllen, K. *Liebigs Ann. Chem.* **1995**, 223. (b) (*E*,*E*)-1,2-bis(tri-*n*-butylstannyl)-ethylene: Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. Panek, J. S.; Masse, C. E. *J. Org. Chem.* **1997**, *62*, 8290. (c) (*Z*)-1,2-bis(tri-*n*-butylstannyl)ethylene: Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755.

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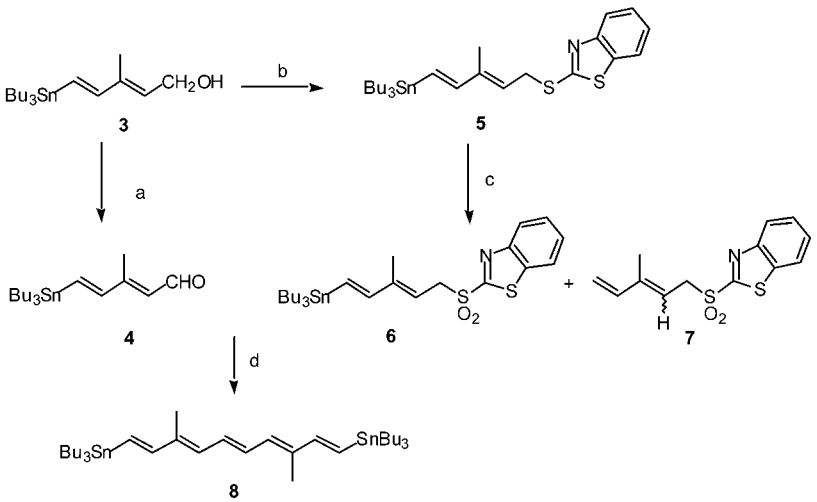
10.1021/jo025727f CCC: $22.00
Published on Web 06/06/2002

SCHEME 1[a]

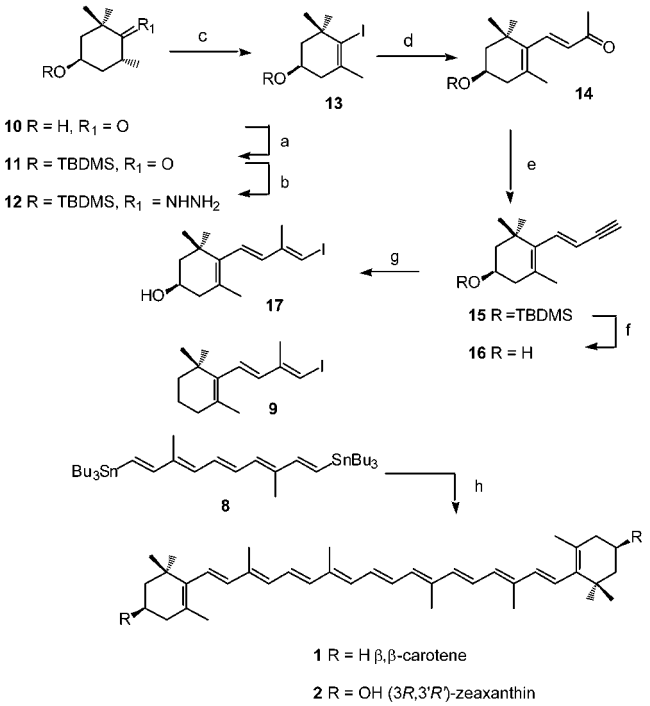


[a] Reagents and reaction conditions: (a) SO_3·Py, Et_3N, CH_2Cl_2/DMSO (1:1), 0 °C (96%), ref 7; (b) BTSH, DIAD, PPh_3, THF, 0 → 25 °C (93%); (c) $Mo_7O_{24}(NH_4)_6$·$4H_2O$, 35% H_2O_2, EtOH, 25 °C (**6**, 61%; **7**, 31%); (d) i. NaHMDS, Et_2O, −78 °C. ii. **4**, THF, −78 → 25 °C (70%).

by conversion of **11** to hydrazone **12**. Oxidation of the latter with iodine according to Barton's procedure[13] afforded cyclohexenyl iodide **13** in 80% overall yield. Heck coupling of **13** with methyl vinyl ketone[14] led in 90% yield to **14**.[12b] The one-pot, three-step procedure for converting methyl ketones to terminal alkynes[11] proceeded uneventfully to afford **15** in 67% yield, which was deprotected to **16** (96%). Alkyne **16** was finally converted to the trienyl iodide **17** in 69% yield by the well-established protocol, a procedure which also yielded trienyl iodide **9** from its precursor dienyne as already described.[11a]

A comprehensive study of the Stille reaction[15,16] was carried out to optimize the stitching reaction of **8** and **9**. The best conditions found involve the use of 4 mol % $(PhCN)_2PdCl_2$ as precatalyst in a THF/DMF mixture in the presence of Hünig's base (3 equiv) and a trace amount of the radical inhibitor BHT. Under these conditions, the coupling of **8** and **9** required 12 h at room temperature, affording *β*-carotene **1** in 73% yield. Farina's conditions [Pd_2dba_3, tris-phenylarsine, NMP][17] were also successful, albeit the yield was lower. Other alternatives proved unsatisfactory: Pd_2dba_3/tris-2-furylphosphine in DMF[16] and $(CH_3CN)_2PdCl_2$ in DMF[15b] led to product deterioration, whereas Pd_2dba_3/tris-2-furylphosphine in THF[17] returned unreacted starting components at ambient temperature. The optimized conditions described above provided the more unstable (3*R*,3′*R*)-zeaxanthin **2**[18] in 46% yield after purification by column chromatography.

SCHEME 2[a]



[a] Reagents and reaction conditions: (a) TBDMSCl, imidazol, DMF, 25 °C (83%); (b) H_2NNH_2·H_2O, Et_3N, EtOH, reflux; (c) I_2, DBN, Et_2O (two steps, 80%); (d) $Pd(PPh_3)_4$ (cat.), MVK, Et_3N, DMF, 75 °C, 12 h (90%); (e) i. LDA, $ClPO(OEt)_2$, −78 °C. ii. LDA, 0 → 25 °C (67%); (f) (^{n}Bu)$_4$NF, THF, 25 °C (96%); (g) i. Me_3Al, Cp_2ZrCl_2, CH_2Cl_2, 25 °C, 12 h. ii. I_2, THF, −40 °C (69%); (h) **9** or **17**, $(PhCN)_2PdCl_2$ (cat.), (^{i}Pr)$_2$NEt, BHT, THF/DMF (1:1), 25 °C (**1**, 73%; **2**, 46%).

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In summary, synthesis of the carotenoid polyene region via σ bond construction has been achieved by a 2-fold Stille cross-coupling of geometrically homogeneous central lynchpin C_{12}-bis-stannane **8** and two units of terminal C_{14}-alkenyl iodides. Work is in progress to develop experimental conditions for monocoupling that could extend the protocol to the preparation of nonsymmetrical carotenoids.

Experimental Section

General Experimental Procedures.[16b] **(2*E*,4*E*)-1-(Benzothiazol-2-yl)-sulfanyl-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene 5.** To a solution of (2*E*,4*E*)-5-(tri-*n*-butylstannyl)-2-methylpenta-2,4-dien-1-ol **3** (0.5 g, 1.29 mmol), 2-mercaptobenzothiazol (0.32 g, 1.94 mmol), and Ph_3P (0.55 g, 2.10 mmol) in THF (8 mL), at 0 °C, was added diisopropyl azodicarboxylate (DIAD) (0.38 mL, 1.94 mmol) in THF (3 mL). After the mixture was stirred for 30 min, the solvent was removed and the residue was purified by chromatography (C-18 silica gel, 85:15 CH_3CN/CH_2Cl_2) to afford 0.64 g (93%) of **5**. ^{1}H NMR (400 MHz, C_6D_6): δ 7.96 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.80 (d, J = 19.3 Hz, $^3J_{Sn-H}$ = 31.6 Hz, 1H), 6.45 (d, J = 19.3 Hz, $^2J_{Sn-H}$ = 33.8 Hz, 1H), 5.79 (t, J = 7.9 Hz, 1H), 4.10 (d, J = 7.9 Hz, 2H), 1.81 (s, 3H), 1.7−1.6 (m, 6H), 1.5−1.3 (m, 6H), 1.3−1.0 (m, 15H). ^{13}C NMR (100 MHz, C_6D_6): δ 166.5, 153.9, 150.5, 140.0, 135.9, 128.3, 126.2, 125.6, 124.3, 121.8, 121.2, 31.9, 29.5, 27.7, 13.9, 11.9, 9.8. MS (FAB$^+$): *m*/*z* (%) 538 (M$^+$+2, 24), 537 (M$^+$+1, 16), 536 (M$^+$, 22), 177 (100). HMRS (FAB$^+$): calcd for $C_{25}H_{40}NS_2118Sn$, 536.1604; found, 536.1618.

(2*E*,4*E*)-1-((Benzothiazol-2-yl)sulfonyl)-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene 6. To a solution of (2*E*,4*E*)-1-((benzothiazol-2-yl)sulfanyl)-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene **5** (0.15 g, 0.28 mmol) in EtOH (3 mL), at 25 °C, was added a solution of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.74 g, 0.06 mmol) in H_2O_2 (35% in H_2O, 2.4 mL, 27.96 mmol). After the mixture was stirred at room temperature for 30 min, aqueous NH_4Cl solution was added, the mixture was extracted with Et_2O (3×) and the organic extracts were washed with water (3×), dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by chromatography (Al_2O_3, 90:10 hexane/ethyl acetate) to afford 0.097 g (61%) of **6** and 0.024 g (31%) of **7.** Data for **6**: ^{1}H NMR (400 MHz, C_6D_6): δ 7.98 (d, J = 8.0 Hz, 1H), 7.0−7.1 (m, 2H), 6.92 (t, J = 7.1 Hz, 1H), 6.68 (d, J = 19.3 Hz, $^2J_{Sn-H}$ = 31.4 Hz, 1H), 6.38 (d, J = 19.3 Hz, $^3J_{Sn-H}$ = 32.7 Hz, 1H), 5.55 (t, J = 8.0 Hz, 1H), 4.11 (d, J = 8.0 Hz, 2H), 1.6−1.8 (m, 6H), 1.66 (s, 3H), 1.2−1.4 (m, 6H), 0.8−1.0 (m, 15H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 151.0, 146.4, 138.8, 132.3, 130.0, 129.8, 129.7, 126.9, 124.8, 117.1, 56.5, 29.7, 28.9, 20.1, 14.9, 11.0. MS (FAB$^+$): *m*/*z* (%) 567 (M$^+$, 10), 177 (100). HRMS (FAB$^+$): calcd for $C_{25}H_{39}NO_2S_2118Sn$, 567.1581; found 567.1596. Data for **7** (major isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.6−7.7 (m, 2H), 6.34 (dd, J = 17.4, 10.7 Hz, 1H), 5.52 (t, J = 8.1 Hz, 1H), 5.21 (d, J = 17.4 Hz, 1H), 5.10 (d, J = 10.7 Hz, 1H), 4.38 (d, J = 8.1 Hz, 2H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 165.7, 152.7, 144.1, 139.5, 137.2, 128.0, 127.5, 125.4, 122.3, 115.4, 114.6, 54.9, 12.2. MS (FAB$^+$): *m*/*z* (%) 279 (M$^+$, 6), 200 (100). HRMS (FAB$^+$): calcd for $C_{13}H_{13}NO_2S_2$ 279.0388; found 279.0387.

(1*E*,3*E*,5*E*,7*E*,9*E*)-1,10-Bis(tri-*n*-butylstannyl)-3,8-dimethyldeca-1,3,5,7,9-pentaene 8. To a solution of (2*E*,4*E*)-1-((benzothiazol-2-yl)sulfonyl)-5-(tri-*n*-butylstannyl)-3-methylpenta-2,4-diene **6** (0.071 g, 0.25 mmol) in THF (4 mL), at −78 °C, was added NaHMDS (1 M in THF, 0.23 mL, 0.23 mmol), and the mixture was stirred for 45 min. A solution of (2*E*,4*E*)-5-(tri-*n*-butylstannyl)-2-methylpenta-2,4-dien-1-al **4** (0.072 g, 0.19 mmol) in THF (4 mL) was added, and the reaction was allowed to reach ambient temperature very slowly for 12 h. Aqueous 1 M NaOH (5 mL) and *t*BuMeO (10 mL) were added. The layers were separated, and the aqueous layer was extracted with *t*BuMeO (3×). The organic extracts were washed with brine (3×) and dried, and the solvent was removed. The residue was purified by chromatography column (C-18 silica gel, 70:30 CH_3CN/CH_2Cl_2) to afford 0.076 g (83%) of **8**. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 6.79 (d, J = 19.2 Hz, 2H), 6.73 (m, 2H), 6.46 (m, 2H), 6.41 (d, J = 19.2 Hz, 2H), 1.90 (s, 6H), 1.5−1.6 (m, 12H), 1.3−1.4 (m, 12H), 0.8−1.0 (m, 30H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 151.9, 138.4, 129.3, 127.4, 127.0, 29.8, 27.9, 14.0, 10.0, 8.3. UV (MeOH): λ_{max} 258, 340, 376. MS (FAB$^+$): *m*/*z* (%) 680 (M$^+$-Bu, 4), 179 (100). HRMS (FAB$^+$): calcd for $C_{36}H_{69}120Sn_2$ 741.3443; found 741.3444.

(4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,2,6-trimethylcyclohexan-1-one 11. To a solution of (4*R*,6*R*)-4-hydroxy-2,2,6-trimethylcyclohexan-1-ona **10** (100 mg, 0.64 mmol) and imidazole (109 mg, 1.6 mmol) in DMF (2 mL), at 0 °C, was added a solution of TBDMSiCl (182 mg, 0.7 mmol) in DMF (2 mL). The reaction was stirred for 6 h and then poured into H_2O (10 mL) and extracted with hexane (3×). The organic layers were washed with H_2O (5×), dried, and evaporated. The residue was purified by chromatography (silica gel, 97:3 hexane/ethyl acetate) to afford 143 mg (83%) of **11**. $[\alpha]^D_{20}$ −65.0 (*c* 0.55, MeOH).[12a]

(*R*)-*tert*-Butyldimethylsilyl 3,5,5-Trimethyl-4-iodocyclohex-3-en-1-yl Ether 13. To a solution of (4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-2,2,6-trimethylcyclohexan-1-one **11** (0.50 g, 1.28 mmol) in ethanol (3.5 mL) at 25 °C, were added $H_2NNH_2{\cdot}H_2O$ (1.6 mL, 33.13 mmol) and Et_3N (0.39 mL, 2.78 mmol). After the mixture was stirred for 24 h at 100 °C, the solvent was removed and the residue was taken in Et_2O (4 mL) and washed with brine (3×). The aqueous layers were extracted with Et_2O (4×), and the organic extracts were dried over Na_2SO_4 and concentrated. To a solution of the residue in Et_2O (7.5 mL) and DBN (2.06 mL, 16.65 mmol) was added a solution of iodine (0.99 g, 3.88 mmol) in Et_2O (7.5 mL). After the mixture was stirred for 15 min, an aqueous saturated $NaHCO_3$ solution was added, the layers were separated, the organic layer was dried over Na_2SO_4, and the solvent was removed. A solution of the residue in C_6H_6 (7.5 mL) was treated with DBN (5 mL). After the mixture was stirred for 2.5 h, it was poured into Et_2O and washed with aqueous $Na_2S_2O_3$ (3×), and the organic layer was dried and evaporated. The residue was purified by chromatography (silica gel, hexane) to afford 0.563 g (80%) of **13**. $[\alpha]^D_{20}$ −29.9 (*c* 1.79, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.8−3.9 (m, 1H), 2.28 (dd, J = 5.6, 2.2 Hz, 1H), 2.24 (dd, J = 5.6, 2.2 Hz, 1H), 1.9−1.8 (1H, m), 1.86 (s, 3H), 1.64 (dd, J = 12.1, 11.9 Hz, 1H), 1.11 (s, 3H), 1.08 (s, 3H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 115.7, 65.1, 46.4, 42.9, 41.4, 34.5, 30.7, 29.3, 25.9, −4.7. MS (EI$^+$): *m*/*z* (%) 380 (M$^+$, 1), 323 (M$^+$ − *t*Bu, 32), 267 (100). HRMS (EI$^+$): calcd for $C_{15}H_{29}IOSi$ 380.1032; found, 380.1022.

[(*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-2,6,6-trimethylcyclohex-1-en-1-yl]but-3-en-2-one 14. To a solution of (*R*)-(*tert*-butyldimethylsilyl) 3,5,5-trimethyl-4-iodocyclohex-3-en-1-yl ether **13** (0.80 g, 2.21 mmol) in DMF (40 mL) was added $Pd(PPh_3)_4$ (0.24 g, 0.21 mmol), and the mixture was degassed by the freeze−thaw method (three cycles). MVK (0.53 mL, 6.31 mmol) and Et_3N (0.88 mL, 6.31 mmol) were then added, and the reaction was heated to 75 °C for 13 h. The mixture was diluted with *t*BuOMe (50 mL), washed with 1% HCl, and extracted with *t*BuOMe (3×). The combined organic layers were washed with aqueous $NaHCO_3$ (3×) and dried (Na_2SO_4), and the solvent was removed. The resulting oil was purified by chromatography (silica gel, 90:10 hexane/AcOEt) affording 615 mg (90%) of **14**.[12b]

(*R*,*E*)-*tert*-Butyldimethylsilyl 4-(But-1-en-3-yn-1-yl)-3,5,5-trimethylcyclohex-3-en-1-yl Ether 15. A solution of LDA was prepared by addition of *n*BuLi (1.67 M, 1.2 mL, 2.00 mmol) to a solution of $(i\text{Pr})_2NH$ (0.28 mL, 2.00 mmol) in THF (5.5 mL). After 30 min at 0 °C, the mixture was cooled to −78 °C and a solution of [(*R*,*E*)-4-*tert*-butyldimethylsilyloxy-2,6,6-trimethylcyclohex-1-en-1-yl]but-3-en-2-one **14** (0.615 g, 1.91 mmol) in THF (2 mL) was added via cannula. The mixture was stirred for 1.5 h at −78 °C, $ClPO(OEt)_2$ (0.288 mL, 2.00 mmol) was added, and the resulting mixture was stirred for 3 h at room temperature. In a separate flask, a solution of LDA was prepared with $(i\text{Pr})_2NH$ (0.60 mL, 4.29 mmol) and *n*BuLi (1.67 M, 2.6 mL, 4.29 mmol) in THF (11 mL), at 0 °C. To this was added the reaction mixture

obtained above, and the resulting solution was stirred at room temperature for 13 h. After cooling the reaction mixture to 0 °C, H_2O was slowly added, followed by extraction with *t*BuOMe (3×). The combined organic layers were washed with 1 M HCl (3×), H_2O (3×), and aqueous saturated $NaHCO_3$ solution (3×) and dried, and the solvent was evaporated. The resulting oil was purified by cromatography (silica gel, 95:5 hexane/AcOEt), to afford 0.37 g (67%) of **15**. $[\alpha]^{D}_{24}$ −28.3 (*c* 0.17, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (d, J = 16.5 Hz, 1H), 5.38 (dd, J = 16.4, 2.1 Hz, 1H), 3.9−3.8 (m, 1H), 2.87 (d, J = 2.2 Hz, 1H), 2.17 (dd, J = 17.5, 5.7 Hz, 1H), 2.00 (dd, J = 17.3, 9.5 Hz, 1H), 1.66 (s, 3H), 1.6−1.5 (m, 1H), 1.4−1.3 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.84 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 136.3, 129.4, 111.5, 83.1, 65.3, 48.7, 43.0, 36.8, 30.0 28.4, 25.9, 21.4, 18.2, −4.6. IR (NaCl): ν 3314, 2100 cm^{-1}. MS (EI$^+$): *m*/*z* (%) 304 (M$^+$, 7), 191 (100). HRMS (EI$^+$): calcd for $C_{19}H_{32}$-OSi 304.2222; found, 304.2226.

(*R*)-4-[(*E*)-But-1-en-3-yn-1-yl]-3,5,5-trimethylcyclohex-3-en-1-ol 16. To a solution of (*R*,*E*)-*tert*-butyldimethylsilyl 4-(but-1-en-3-yn-1-yl)-3,5,5-trimethylcyclohex-3-en-1-yl ether **15** (0.066 g, 0.22 mmol) in THF (2.2 mL) was added (nBu)$_4$NF (1.0 M in THF, 0.32 mL, 0.32 mmol), and the mixture was stirred for 2.5 h at room temperature. It was poured over aqueous satured $NaHCO_3$ solution, extracted with *t*BuOMe (3×), and dried ($NaSO_4$), and the solvent was evaporated. The residue was purified by chromatography (silica gel, 80:20 hexane/AcOEt), affording 0.041 g (96%) of **16**. $[\alpha]^{D}_{24}$ −94.6 (*c* 0.66, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (d, J = 16.4 Hz, 1H), 5.42 (dd, J = 16.4, 2.1 Hz, 1H), 3.9−3.8 (m, 1H), 2.92 (d, J = 2.2 Hz, 1H), 2.35 (dd, J = 17.1, 5.5 Hz, 1H), 2.0−1.9 (m, 1H), 1.71 (s, 3H), 1.8−1.7 (m, 1H), 1.5−1.4 (m, 1H), 1.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 136.5, 128.7, 111.8, 82.9, 77.4, 64.8, 48.3, 42.4, 36.8, 29.7, 28.5, 21.3. IR (NaCl):ν 3600−3100, 2099 cm^{-1}. MS (FAB$^+$): *m*/*z* (%) 191 (M$^+$, 100). HRMS (FAB$^+$): calcd for $C_{13}H_{19}O$ 191.1436; found, 191.1431.

(*R*)-4-[(*E*,*E*)-4-Iodo-3-methylbut-1,3-dien-1-yl]-3,5,5-trimethylcyclohex-3-en-1-ol 17. To a solution of Cp_2ZrCl_2 (0.081 g, 0.28 mmol) in CH_2Cl_2 (1 mL), at 0 °C, were sequentially added Me_3Al (0.080 mL, 0.83 mmol) and a solution of (*R*)-4-[(*E*)-but-1-en-3-yn-1-yl]-3,5,5-trimethylcyclohex-3-en-1-ol **16** (0.053 g, 0.28 mmol) in CH_2Cl_2 (1 mL). After the reaction mixture was stirred for 12 h at room temperature, it was cooled to −40 °C and a solution of iodine (0.21 g, 0.83 mmol) in THF (1.5 mL) was added. After addition of THF/H_2O (1:1, v/v) the mixture was extracted with *t*BuOMe (3×), the extracts were dried, and the solvent was evaporated. The residue was purified by cromatography (silica gel, 80:20 hexane/AcOEt) affording 0.064 g (69%) of **17**. $[\alpha]^{D}_{22}$ −105.8 (*c* 0.135, MeOH). ^{1}H NMR (400 MHz, C_6D_6): δ 6.1−5.9 (m, 3H), 3.9−3.8 (m, 1H), 2.20 (dd, J = 17.0, 5.5 Hz, 1H), 1.94 (dd, J = 17.0, 9.6 Hz, 1H), 1.84 (s, 3H), 1.7−1.6 (m, 1H), 1.57 (s, 3H), 1.42 (t, J = 11.8 Hz, 1H), 0.97 (s, 6H). ^{13}C NMR (100 MHz, C_6D_6): δ 145.4, 137.2, 134.9, 127.4, 127.0, 83.2, 64.6, 48.6, 42.7, 36.9, 30.3, 28.7, 21.6, 19.9. IR (NaCl): ν 3600−3100 cm^{-1}. MS (EI$^+$): *m*/*z* (%) 332 (M$^+$, 100). HRMS (EI$^+$): calcd for $C_{14}H_{21}IO$ 332.0637; found, 332.0637.

(3*R*,3′*R*)-Zeaxanthin 2. General Procedure for Stille Cross-Coupling. To a solution of (*R*)-4-[(*E*,*E*)-4-iodo-3-methylbut-1,3-dien-1-yl]-3,5,5-trimethylcyclohex-3-en-1-ol **17** (0.023 g, 0.069 mmol) and $(PhCN)_2PdCl_2$ (3.0 mg, 0.008 mmol) in DMF (1.2 mL) was added a solution of (1*E*,3*E*,5*E*,7*E*,9*E*)-1,10-bis(tri-*n*-butylstannyl)-3,8-dimethyldeca-1,3,5,7,9-pentaene **8** (0.019 g, 0.026 mmol) in THF (1.2 mL), followed by (iPr)$_2$NEt (0.027 mL, 0.158 mmol) and one drop of a diluted BHT solution. The reaction was stirred at room temperature in the dark for 16 h and then poured into aqueous KF solution. The mixture was extracted with CH_2Cl_2 (3×), the organic layers were washed with H_2O (3×) and dried, and the solvent was evaporated. The residue was purified by chromatography (neutral alumina Act. II, gradient 100 CH_2Cl_2 → 97:3 CH_2Cl_2:MeOH) and recrystallization (mp 158−162 °C, hexane/AcOEt) to afford 6 mg (46%) of **2**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.7−6.6 (m, 4H), 6.35 (d, J = 15.0 Hz, 2H), 6.25 (d, J = 5.9 Hz, 2H), 6.14 (d, J = 12.5 Hz, 2H), 6.2−6.1 (m, 4H), 4.1−4.0 (m, 2H), 2.37 (dd, J = 16.5, 5.2 Hz, 2H), 2.1−2.0 (m, 2H), 1.97 (s, 12H), 1.8−1.7 (m, 2H), 1.7 (s, 6H), 1.6−1.4 (m, 2H), 1.07 (s, 12H). MS (FAB$^+$): *m*/*z* (%) 568 (M$^+$, 45), 154 (100). HRMS (FAB$^+$): calcd for $C_{40}H_{57}O_2$ 569.4359; found, 569.4361.[1b,18]

***β*,*β*-Carotene 1.** Following the general procedure for Stille cross-coupling, the title compound was obtained in 73% yield after purification by chromatography (neutral alumina Act II, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.7−6.6 (m, 4H), 6.29 (d, J = 14.9 Hz, 2H), 6.2−5.9 (m, 8H), 1.96 (t, J = 5.7 Hz, 4H), 1.91 (s, 6H), 1.66 (s, 6H), 1.6−1.5 (m, 8H), 1.20 (s, 6H), 0.97 (s, 12H). MS (EI$^+$): *m*/*z* (%) 536 (M$^+$, 56), 69 (100). HRMS (EI$^+$): calcd for $C_{40}H_{56}$ 536.4382; found, 536.4386.[4]

Acknowledgment. We thank Xunta de Galicia (Grant PGIDT99 PX30105B) and MCYT (Grant SAF98-0143, FPU fellowship to B. Vaz) for financial support, and Dr. Michelangelo Scalone (F. Hoffman-La Roche, Basel) for a generous gift of starting material (*R*)-**10**.

Supporting Information Available: Spectroscopic characterization and copies of ^{1}H NMR/^{13}C NMR spectra of the compounds described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025727F