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Synthesis of C15,C14′-ring locked all-*trans*-β-carotene

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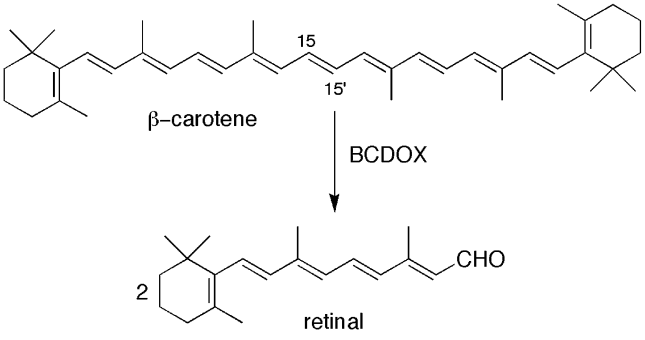
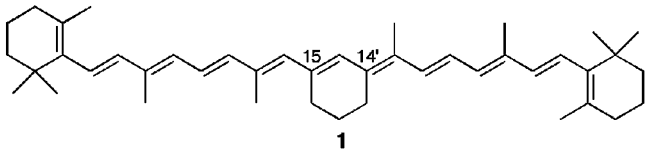
Abstract—Synthesis of C15,14′-ring locked all-*trans*-β-carotene is described. The symmetric nature of the β-carotene analog allowed for rapid construction of the carbon frame through bis-olefination of the central dialdehyde containing the ring functionality with a C15 ylide bearing the ionone moiety.

Vitamin A and its derivatives (retinoids) are not only essential components in vision,[1,2] but also they exert multiple effects on cell differentiation and development with important clinical implications.[3–6] β-Carotene-15,15′-dioxygenase (BCDOX) is the enzyme responsible for the oxidative cleavage of β-carotene to retinal in animals (Scheme 1).[7,8] Its function is of utmost importance since vertebrates cannot biosynthesize retinoids and must rely on dietary intake or oxidation of β-carotene to supplement their needs. Despite its pivotal role in the production of retinoids, BCDOX has been a largely forgotten enzyme. However, recent discovery of genes responsible for production of BCDOX in various species has re-ignited research in this area.[9]

Our interest in BCDOX stems from its unique ability to selectively oxidize the central double bond in β-carotene either as a dioxygenase or a monooxygenase.[9–11] In particular, we are interested in labeling studies that will enable us to determine the exact source of oxygen in the products; i.e. do both oxygen atoms in a single cleavage event come from the same molecular oxygen. The cleavage of β-carotene yields two molecules of retinal, and thus the loss in molecular connectivity does not allow for analysis of products obtained from a single oxidation event in isotopic labeling studies. Therefore, we plan to use the β-carotene analog **1** for these studies. Compound **1** contains a ring within the target olefin and will preserve the molecular connectivity of the original molecule upon oxidative cleavage. Herein, we describe the convergent synthesis of the all-*trans*-C15,C14′-ring locked β-carotene analog **1**.



Scheme 1.



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The retrosynthetic approach depicted in Scheme 2 entails the bis-coupling the C15 ylide **2** with the C13 dialdehyde **3**. The C13-dialdehyde segment is stereoselectively constructed by sequential Wittig and HWE reactions starting from cyclohexenone-3-carboxaldehyde (**5**). The C15-ylide is obtained from β-ionone **4**, as described previously.[12]

Synthesis of 2-methyl-3-[3-(1-methyl-2-oxo-ethylidene)-cyclohex-1-enyl]-propenal **3**, depicted in Scheme 3, began with securing cyclohexenone-3-carboxaldehyde **5**, which was prepared by previously reported procedures.[13] Olefination of **5** with diethyl(1-cyanoethyl)phosphonate afforded the dicyanide **6** in good yield as a ~2:1 mixture of *EE*/*EZ* isomers.[14] The simultaneous reduction of the two cyanide groups in **6**

Keywords: β-carotene; β-carotene-15,15′-dioxygenase; Wittig; HWE reactions.

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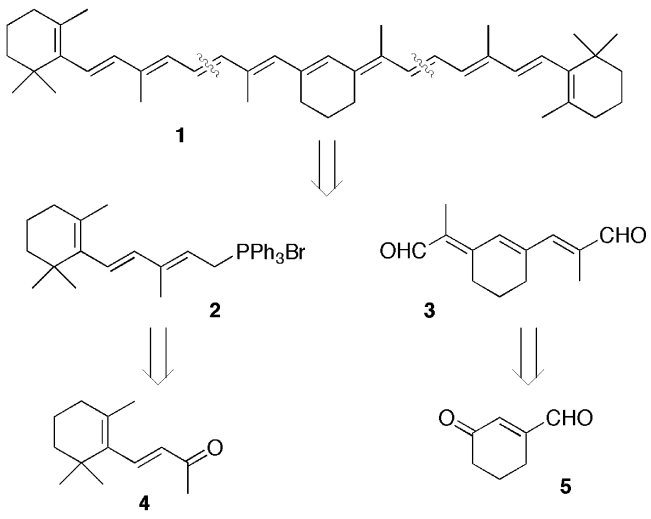
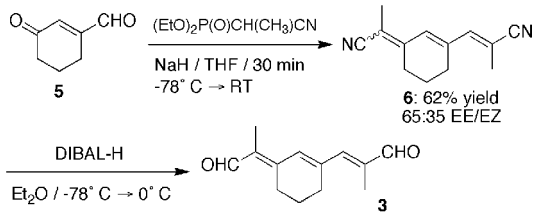


Scheme 2.



Scheme 3.

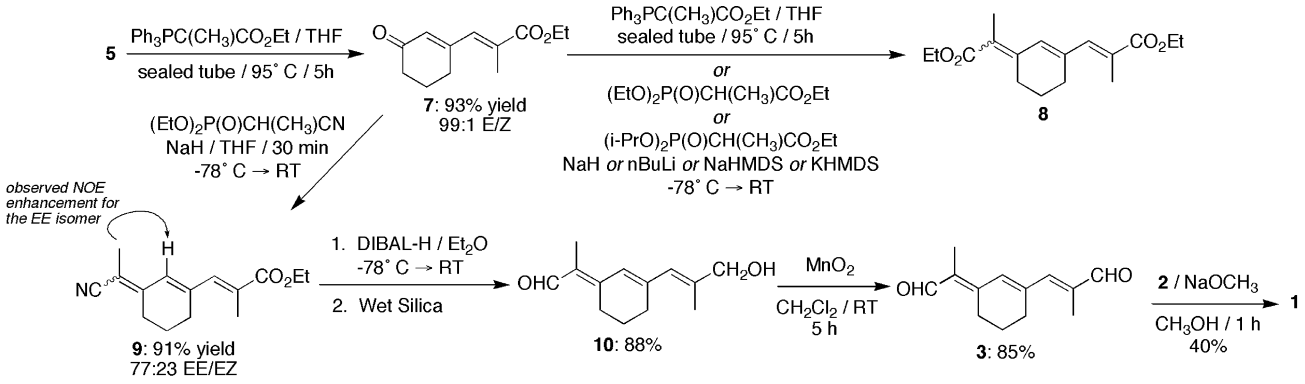
with DIBAL-H did not lead to a satisfactory yield of the dialdehyde as the transformation led mostly to decomposition of the starting material (various conditions).

In order to overcome this problem, we turned our attention to the synthesis of diester **8** (Scheme 4). Treatment of cyclohexenone-3-carboxaldhyde **5** with (carbethoxyethylidene)-triphenylphosporane provided compound **7** in 93% yield (*E*/*Z* 99:1).[15] However, the single pot conversion of **5** to **8**, utilizing excess of ylide was not successful. For that matter, subjecting the ketoester **7** to a second round of Wittig or HWE olefination with ethyl 2-(diethylphosphono)propionate or ethyl 2-(diisopropylphosphono)propionate with various bases under different reaction conditions (NaH, *n*BuLi, KHMDS, and NaHMDS at −78°C or rt) did not yield the desired diester **8**. This is presumably due to the reaction of the ylide with a less reactive conjugated carbonyl, and the formation of a tetrasubstituted olefin, which is sterically a cumbersome and difficult task for a typical HWE process.

Diethyl(1-cyanoethyl)phosphonate is a sterically less demanding ylide (as compared to the ester analog of the same) and could be better suited to deliver the tetrasubstituted olefin. Gratifyingly, the HWE reaction of the ketoester **7** with diethyl(1-cyanoethyl)phosphonate in the presence of NaH afforded the cyanoester **9** in excellent yield as a >3:1 mixture of *EE*/*EZ* isomers.[16] The geometry of the new olefinic bond was confirmed by NOE experiments. In particular, compound **9** showed a strong enhancement of the C3-methyl group upon irradiation of the ring olefinic proton for the *EE* isomer. The same enhancement was not observed for the *EZ* isomer (Scheme 4).

The reduction of both the ester and cyano groups in **9** could be carried out in one step by using excess DIBAL-H, however, the yields and recovery of the product were not optimum. Therefore, we opted to modify the procedure slightly by reducing both functionalities sequentially without isolating the intermediate compound. The reaction was initiated by the addition of DIBAL-H (2 equiv.) to the solution of **9** at −78°C. A second dose of DIBAL-H (2 equiv.) was added in 15 min, while the solution was kept at −78°C. After 45 min, the reaction mixture was allowed to warm up to 0°C. Wet silica gel was used to quench the reaction by vigorously stirring the slurry (4 h), followed by filtration of the silica. Subsequent treatment of the filtrate with sodium-potassium tartrate afforded the allylic alcohol **10** in 85% yield.[17] Oxidation of **10** with freshly prepared activated manganese dioxide furnished the dialdehyde **3** in good yields.[18]

With **3** in hand the stage was set for the double olefination with C15-triphenyl phosphonium bromide **2**. Treatment of **2** with sodium methoxide followed by addition of dialdehyde **3** secured compound **1** in a moderate yield (40% Scheme 4).[19] Isomeric contaminations were purified by HPLC. In conclusion, we have synthesized an unnatural C15,14′-ring locked analog of



Scheme 4.

β-carotene. Studies on enzymatic oxidation will be reported in due course.

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14. *3-[3-(1-Cyano-ethylidene)-cyclohex-1-enyl]-2-methyl-acrylonitrile* (**6**): [*EE*-isomer] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (1H, s), 6.56 (1H, s), 2.70 (2H, t, $J=6.00$ Hz, CH_2), 2.35 (2H, t, $J=6.30$ Hz, CH_2), 2.07 (3H, s, CH_3), 1.95 (3H, s, CH_3), 1.78 (2H, quintet, $J=6.60$, 6.30 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.07, 145.64, 141.22, 132.47, 119.26, 119.22, 106.85, 105.19, 25.74, 25.61, 22.79, 21.3, 16.17. HRMS: calcd for $C_{13}H_{14}N_2$ 198.1157; found 198.1162. [*EZ*-isomer]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.59 (1H, s), 6.50 (1H, s), 2.66 (2H, t, $J=6.00$ Hz, CH_2), 2.58 (2H, t, $J=6.30$ Hz, CH_2), 2.07 (3H, s, CH_3), 1.96 (3H, s, CH_3), 1.79 (2H, quintet, $J=6.46$, 6.30 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.59, 145.28, 141.96, 128.69, 119.94, 119.03, 107.33, 104.44, 29.25, 26.64, 22.69, 21.75, 15.12. HRMS: calcd for $C_{13}H_{14}N_2$ 198.1157; found 198.1160.
15. *2-Methyl-3-(3-oxo-cylcohex-1-enyl)-acrylic acid ethyl ester* (**7**): [*E*-isomer] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (1H, s), 6.00 (1H, s), 4.2 (2H, q, $J=6.90$ Hz), 2.43–2.38 (4H, m, 2×CH_2), 2.05–2.01 (2H, m, CH_2), 2 (3H, s, CH_3), 1.28 (3H, t, $J=6.90$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.25, 167.57, 156.51, 137.10, 132.36, 129.52, 61.09, 37.14, 29.45, 22.57, 14.59, 14.04. HRMS: calcd for $C_{12}H_{16}O_3$ 208.1099; found 208.1093. [*Z*-isomer] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 (1H, s), 5.83 (1H, s), 4.20 (2H, q, $J=6.90$ Hz), 2.31–2.36 (4H, m, 2×CH_2), 2.05–1.93 (2H, m, CH_2), 1.99 (3H, s, CH_3), 1.25 (3H, t, $J=6.90$ Hz).
16. *3-[3-(Cyano-ethylidene)-cyclohex-1-enyl]-2-methyl-acrylic acid ethyl ester* (**9**) [*EE*-isomer]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (1H, s), 6.53 (1H, s), 4.20 (2H, q, $J=7.20$ Hz), 2.60 (2H, dt, $J=1.50$, 6.30 Hz, CH_2), 2.43 (2H, t, $J=6.00$ Hz, CH_2), 2.05 (3H, s, CH_3), 1.95 (3H, s, CH_3), 1.78 (2H, quintet, $J=6.30$ Hz, CH_2), 1.29 (3H, t, $J=7.20$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.50, 148.94, 144.05, 139.42, 129.62, 127.07, 120.27, 102.81, 60.98, 29.36 (2C), 22.26, 15.00, 14.64, 14.20. HRMS: calcd for $C_{15}H_{19}NO_2$ 245.1416; found 245.1423. [*EZ*-isomer]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (1H, s), 6.81 (1H, s), 4.20 (2H, q, $J=7.20$ Hz), 2.39–2.35 (4H, m, 2×CH_2), 2.07 (3H, s, CH_3), 1.93 (3H, s, CH_3), 1.77 (2H, quintet, $J=6.30$ Hz, CH_2), 1.29 (3H, t, $J=7.20$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.53, 150.36, 142.87, 139.27, 130.45, 129.43, 119.58, 103.29, 60.96, 28.89, 25.82, 21.82, 16.02, 14.67, 14.24. HRMS: calcd for $C_{15}H_{19}NO_2$ 245.1416; found 245.1416.
17. *2-[3-(3-Hydroxy-2-methyl-propenyl)-cyclohex-2-enylidene]-propionaldehyde* (**10**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.20 (1H, s), 6.59 (1H, s), 6.10 (1H, s), 4.10 (2H, s), 2.88 (2H, dt, $J=1.20$, 6.30 Hz), 2.44 (2H, t, $J=6.00$ Hz), 1.92 (3H, s, CH_3), 1.85–1.81 (2H, m), 1.84 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.10, 151.52, 147.39, 140.32, 128.94, 126.57, 126.34, 68.67, 30.33, 24.41, 22.75, 16.25, 9.91. HRMS: calcd for $C_{13}H_{18}O_2$ 206.1307; found 206.1308.
18. *2-Methyl-3-[3-(1-methyl-2-oxo-ethylidene)-cyclohex-1-enyl]-propenal* (**3**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.24 (1H, s), 9.46 (1H, s), 6.93 (1H, s), 6.81 (1H, s), 2.90 (2H, dt, $J=6.30$, 1.20 Hz), 2.6 (2H, t, $J=6.00$ Hz), 2.01 (3H, s, CH_3), 1.87 (3H, s, CH_3), 1.89–1.84 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.42, 191.1, 150.74, 148.96, 144.64, 138.93, 133.33, 132.22, 29.29, 24.15, 22.48, 11.31, 10.26. HRMS: calcd for $C_{13}H_{16}O_2$ 204.1150; found 204.1135.
19. **1**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10–5.90 (12H, m, olefinic), 2.55–2.40 (4H, m, 2×CH_2), 2.10 (3H, s, CH_3), 2.20–2.00 (4H, m, 2×CH_2), 1.90 (6H, s, 2×CH_3), 1.78 (3H, s, CH_3), 1.70 (6H, s, 2×CH_3), 1.62–1.59 (4H, m, 2×CH_2), 1.52 (2H, s, CH_2), 1.50–1.42 (4H, 2×CH_2), 1.02 (12H, s, 4×CH_3). HRMS calcd for $C_{43}H_{60}$ 576.4695; found 576.4719. UV: λ_{max} (pentane): 450 nm.