Partial Synthesis of (3*R*,6′*R*)-α-Cryptoxanthin and (3*R*)-*β*-Cryptoxanthin from (3*R*,3′*R*,6′*R*)-Lutein†

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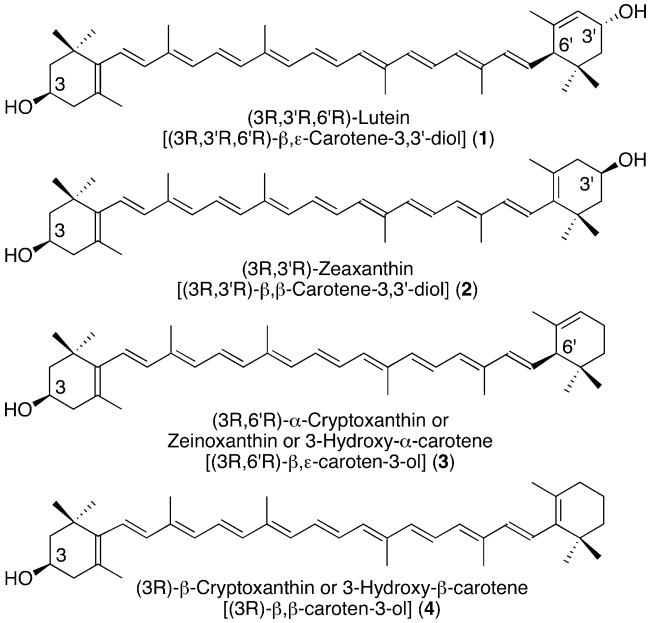
(3*R*,3′*R*,6′*R*)-Lutein (**1**), (3*R*,3′*R*)-zeaxanthin (**2**), (3*R*,6′*R*)-α-cryptoxanthin (**3**), and (3*R*)-*β*-cryptoxanthin (**4**) are among dietary hydroxycarotenoids that have been identified in human serum, milk, and ocular tissues. While **1** containing 6% of **2** is commercially available, industrial production of optically active **3** and **4** has not yet been accomplished. Several processes have been developed that transform **1** into **3**, **4**, and minor quantities of (3*R*,5′*RS*,6′*R*)-3′,4′-didehydro-5′,6′-dihydro-*β*,*β*-caroten-3-ol (**5**) (a regioisomer of **3**). In one process, lutein (**1**) was cleanly deoxygenated to **3** in the presence of trifluoroacetic acid (TFA) and $Me_3N{\cdot}BH_3$ in CH_2Cl_2 at ambient temperature in nearly 90% yield. Reaction of lutein (**1**) with a Lewis acid ($AlCl_3$, $ZnBr_2$, ZnI_2) and a hydride donor ($Me_3N{\cdot}BH_3$, $Na[BH_3(OCOCF_3)]$, $NaCNBH_3$) in solvents such as CH_2Cl_2, THF, and TBME produced similar results. In a two-step process, high-temperature acid-catalyzed dehydration of **1** (propanol/water/acid, 90 °C) gave a mixture of anhydroluteins **6**, **7**, and **8** in 86% yield. In the second step, these dehydration products underwent ionic hydrogenation with TFA/$Me_3N{\cdot}BH_3$ in CH_2Cl_2 to afford a mixture of **3** and **4** in nearly 80% yield that contained only 1% of **5**.

(3*R*,3′*R*,6′*R*)-Lutein (**1**), (3*R*,3′*R*)-zeaxanthin (**2**), (3*R*,6′*R*)-α-cryptoxanthin (**3**), and (3*R*)-*β*-cryptoxanthin (**4**) are among the dietary hydroxycarotenoids that are present in common fruits and vegetables[1,2] as well as in human plasma,[3,4] breast milk,[4] organs/tissues,[5] and ocular tissues.[6−9] Epidemiological and experimental studies suggest that lutein and zeaxanthin, which are the only carotenoids found in the human macula, play an important role in the prevention of age-related macular degeneration (AMD).[10,11] However, a range of dietary carotenoids including α-cryptoxanthin and *β*-cryptoxanthin are present in the human ciliary body that may protect this tissue against ocular diseases such as presbyopia and glaucoma by an antioxidant mechanism.[8] Further, high plasma concentrations of **4** and several other carotenoids in human subjects have been associated with reduction in blood pressure in an Oxford University large intervention trial.[12] Inflammatory markers such as C-reactive protein and fibrinogen have also been linked to low serum levels of **4**.[13] Several studies have investigated the effect of **4** on bone growth and the inhibition of bone resorption in rodents.[14,15] An *in vitro* study has also revealed a positive effect of **4** on increasing bone calcium and enhancing bone alkaline phosphatase.[16] Compound **4** is a precursor of vitamin A and can impart its biological activity in humans by this function. Although **3** has no vitamin A activity, because of its structural similarities to **4** and **1**, it can exert its biological properties by mechanisms of action that are known for non-vitamin A active carotenoids.[17] Therefore, commercial availability of **3** and **4** will allow investigators to evaluate the efficacy of these dietary carotenoids in disease prevention.

In nature, **3** and **4** are among the rare carotenoids, and consequently, their isolation from natural products on an industrial scale is not economically viable. Alternatively, **3** and **4** can be prepared by total or partial synthesis, and researchers have reported the total synthesis of optically inactive **3**[18] and **4**.[18,19] The total synthesis of optically active (3*R*)-*β*-cryptoxanthin-*β*-D-glucopyranoside has also been reported.[20] However, these synthetic methodologies involve numerous steps and are, therefore, quite costly and difficult to implement on an industrial scale. Optically active **3** has also been prepared by partial synthesis from **1**.[21] According to this procedure, **1** is first treated with a pyridine/sulfur trioxide complex, and the resulting sulfate monoester is reduced with lithium aluminum hydride to give **3**; the yield and details of the reaction conditions were not provided. The application of this method to industrial production of **3** is not readily feasible because of the air-sensitive nature of the reagent and the fact that LAH reaction of carotenoids has to be conducted under controlled conditions to avoid the formation of side products. In addition, the reagent used in this reaction cannot afford **4** from **1**. Therefore, there is currently no efficient methodology that can produce optically active **3** and **4** by simple and economically viable processes.



Here we describe an industrially viable single-step process for transforming commercially available **1** directly into optically active **3** in high yield by allylic deoxygenation with a strong acid and a variety of hydride ion donors. In addition, a two-step process consisting of acid-catalyzed dehydration followed by ionic hydro-

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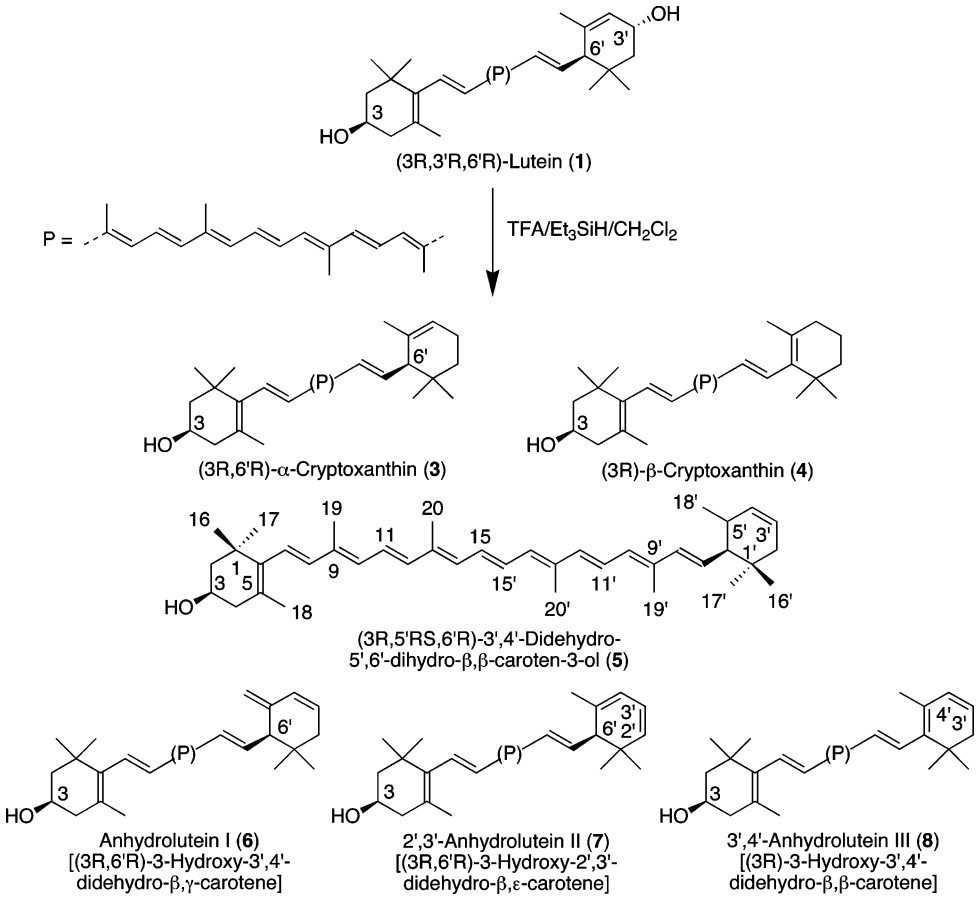
Scheme 1. Allylic Deoxygenation of (3*R*,3′*R*,6′*R*)-Lutein with Et_3SiH/TFA



genation has been developed that can transform lutein into a mixture of optically active α-cryptoxanthin and *β*-cryptoxanthin in which the latter is obtained as the major product.

Results and Discussion

To accomplish the partial synthesis of **3** and **4** from **1**, our initial strategy was to develop an efficient methodology for allylic deoxygenation of **1** at the 3′-position under mild reaction conditions. We rationalized that this transformation would be followed by isomerization of the isolated 4′ bond in **3** to a conjugated double bond at position 5′ to yield **4**. The only known example of the allylic deoxygenation of carotenoids is that of **1**, which has been carried out with a combination of pyridine/sulfur trioxide complex and LAH.[21] In contrast, the base-catalyzed double-bond isomerization of the isolated double bonds in carotenoids such as **1**[22,23] and its epimer, (3*R*,3′*S*,6′*R*)-lutein (3′-epilutein),[24,25] has been well-documented. Therefore, employing similar conditions, **3** could serve as a precursor to **4**.

There are numerous reports in the literature on the synthetic usefulness of "ionic hydrogenation" of C═C, C═O, and C═N multiple bonds and, in a number of cases, for single bonds such as C−OH and C−halogen. For a review of the application of ionic hydrogenation to organic synthesis see the publication by Kursanov et al.[26] In these reactions, the combination of trifluoroacetic acid (TFA) and triethylsilane (Et_3SiH) has been shown to be most convenient and useful due to the reducing ability, handling, and inexpensive nature of the latter reagent. For example, the TFA/Et_3SiH/NH_4F system has been shown to conveniently promote the ionic hydrogenation of ketones, alcohols, and alkenes.[27] Therefore, we focused our initial efforts on the allylic deoxygenation of **1** with TFA/Et_3SiH. Lutein (**1**) is isolated from extracts of marigold flowers and is purified to 85% (wt %) by crystallization and contains 6% zeaxanthin.[28] Since our overall objective was to develop a methodology that can be applied to the industrial production of **3** and **4** from commercially available **1**, no attempt was made to further purify this starting material prior to use.

As shown in Scheme 1, the reaction of **1** with TFA/Et_3SiH in CH_2Cl_2 led to a mixture of carotenoids, which were separated by semipreparative HPLC and identified from their UV−visible, MS, and NMR spectra as **3**, **4**, (3*R*,5′*RS*,6′*R*)-3′,4′-didehydro-5′,6′-dihydro-*β*,*β*-caroten-3-ol (**5**), and anhydroluteins I (**6**), II (**7**), and III (**8**). In addition, **2** that was present in the starting material remained unchanged in the course of the reaction.

The compositions of carotenoids in the crude products of this reaction carried out under different conditions were determined by HPLC and are shown in Table 1 (Supporting Information). HPLC studies of the progress of this reaction revealed that in the presence of TFA **1** rapidly underwent acid-catalyzed dehydration to form **6** as the major product and **7** and **8** as the minor products. Subsequently, these dehydration products reacted slowly with TFA/Et_3SiH to afford **3**, **4**, and **5**. To drive this reaction to completion, 6 equiv of TFA to **1** was needed. However, this high concentration of TFA resulted in degradation and considerable *E*/*Z* isomerization of the products.

As shown in Table 1 (Supporting Information), the optimum molar equivalence of the starting materials for this reaction was TFA/Et_3SiH/**1** = 3−3.5:2:1. Even under these conditions, approximately 15−25% of the *all-E*-carotenoids isomerized to their *Z*-isomers. The formation of **3**, **4**, and **5** can be explained by protonation of **6**, **7**, and **8** with TFA to form a number of resonance hybrid carbocation intermediates that are reduced by Et_3SiH to form the observed products. When acid-catalyzed dehydration of **1** was carried out in the absence of Et_3SiH, **6** (79%) was the major product and **7** (9%) and **8** (12%) were the minor products. Nonetheless, further reaction of this mixture with TFA/Et_3SiH gave **3**, **4**, and **5** in nearly the same ratios that were obtained in the one-pot allylic

deoxygenation of **1** with these reagents. Further, when purified **3** was allowed to react with TFA, no isomerization of this carotenoid to **4** or **5** was achieved. These observations suggest that in ionic hydrogenation of **1** with TFA/Et_3SiH, **3**, **4**, and **5** are formed from carbocation intermediates that result from protonation of **6**, **7**, and **8**. The protonation of either **6** or **7** results in the formation of resonance hybrid carbocations that can lead to **3**, while **4** can be formed only from the carbocation that is obtained from protonation of **8**. The fact that substantial amounts of **4** are formed, even though **8** is the minor dehydration product of **1**, suggests that ionic hydrogenation is accompanied by acid-catalyzed isomerization of **6** to **8**.

We have previously isolated and characterized anhydroluteins **6** and **7** from human plasma and have proposed that these carotenoids are most likely formed in the human digestive system from **1** in the presence of acids.[29] Meantime, **6** has also been prepared by Buchecker et al. from allylic reduction of **1** with an $AlCl_3/LiAlH_4$ (3:1) ($AlHCl_2$) complex that, according to the authors, resulted in the formation of **5** as a side product.[30] However, no NMR data and proof of structure for **5** were provided. In the present study, **5** was characterized from its UV−vis, MS, and ^1H and ^{13}C NMR spectra. The UV−visible spectrum of **5** in hexane with the main absorption maximum at 446 nm was consistent with a chromphore identical to that of **1**, **3**, **6**, and **7**. All of these carotenoids have 10 conjugated double bonds with nine located in their polyene chains and the tenth in one of their end-groups. The mass spectrum of **5** with a molecular radical cation at *m/z* 552.50 (100%) (calculated for $C_{40}H_{56}O$) indicated that this compound was isomeric to **3**. The location of the isolated double bond in **5** was determined by NMR analysis. The chemical shifts of the protons and carbons (C1−C18) in the left half of **5** were readily assigned by comparison with those of the published values for **2** and were further confirmed by HSQC and DQF-COSY analysis.[31] The chemical shifts of protons and carbons (C1′−C18′) on the right half of **5**, which has been designated primed numbers, were then based on the NMR data obtained from DEPT-135, HSQC, DQF-COSY, and HMBC experiments. The DEPT-135 experiment indicated the presence of eight quaternary carbons in **5**, and the chemical shifts (δ) of these carbons were in agreement with the proposed structure: C-1′ (32.89), C-1 (37.13), C-5 (126.15), C-9′ (135.61), C-9 (135.75), C-13′ (136.31), C-13 (136.58), and C-6 (137.77). The proton and carbon chemical shifts for the left side end-group and the polyene chain of **5** were identical to those reported by Englert et al.[31] However, the proton signal for Me-18′ in the right side end-group of **5** appeared as a doublet ($J_{18',5'} = 7.7$ Hz) at δ 0.86 and H-5′ as a broad signal at δ 2.51; these data established the location of the double bond and the reduced bond in **5**.

The major difficulty with transformation of **1** to **3** appeared to be the sensitivity of the allylic hydroxyl group in the former to strong acidic conditions, which resulted in the elimination of H_2O and the formation of anhydroluteins **6**−**8**. In addition, Et_3SiH did not serve as a suitable hydride ion donor since it reacted very sluggishly with the carbocation intermediates, and this in turn led to isomerization and degradation of the products due to prolonged exposure to TFA.

To circumvent these problems, we examined the reductive deoxygenation of **1** with $Me_3N{\cdot}BH_3$/TFA and $Me_3N{\cdot}BH_3/AlCl_3$ since amine-boranes have been used in asymmetric reduction of ketones in the presence of acids.[32] As shown in Table 2 (Supporting Information), allylic deoxygenation of **1** in both cases afforded **3** in excellent yields (≥90%) under mild conditions with no significant *E/Z*-isomerization. Other amine-boranes such as $Me_2NH{\cdot}BH_3$ and $Me_3CNH_2{\cdot}BH_3$ were also shown to be effective as hydride donors in this reaction. As expected, the nonallylic hydroxyl group in **1** at the 3 position remained intact and was not altered by these reagents.

Encouraged by this finding, we then examined the reaction of **1** with combinations of $NaCNBH_3$ and ZnI_2, $ZnBr_2$, or $ZnCl_2$ because these reagents have been successfully employed in reductive deoxygenation of allylic and benzylic alcohols, α,β-unsaturated ketones, and aryl ketones.[33,34] The reaction of **1** with $NaCNBH_3/ZnI_2$ gave a 90% isolated yield of **3** after crystallization, while with $ZnBr_2$ the isolated yield was 75%, and with $ZnCl_2$ only 26% of **3** was formed after 24 h at room temperature (Table 2, Supporting Information).

To avoid the use of toxic $NaCNBH_3$, we also examined the reductive deoxygenation of **1** with other hydride donors such as $NaBH_4$ and sodium acyloxyborohydrides in combination with ZnI_2 or $ZnBr_2$ (Table 2, Supporting Information).

Among these, $Na[BH_3(OCOCF_3)]$ when used with $ZnBr_2$ was shown to yield **3** from **1** in 93% isolated yield under mild reaction conditions. Sodium acyloxyborohydrides, prepared from $NaBH_4$ and a carboxylic acid, have also been shown to promote the reduction of carboxamides to the corresponding amines.[35] The superiority of $Na[BH_3(OCOCF_3)]$ to $Na[BH_3(OCOCH_3)]$ as a hydride donor was demonstrated in the reduction of tertiary amides. This was consistent with our finding that while **1** did not react with $Na[BH_3(OCOCH_3)]/ZnI_2$, it was readily reduced to **3** with $Na[BH_3(OCOCF_3)]/ZnI_2$ in an excellent yield under mild reaction conditions.

Having developed several convenient and industrially viable methodologies for partial synthesis of optically active α-cryptoxanthin (**3**) from lutein (**1**), we attempted the base-catalyzed isomerization of **3** to arrive at β-cryptoxanthin (**4**). However, employing conditions similar to those reported for the transformation of lutein to zeaxanthin (**2**), isomerization of **3** to **4** could not be achieved.[22,23]

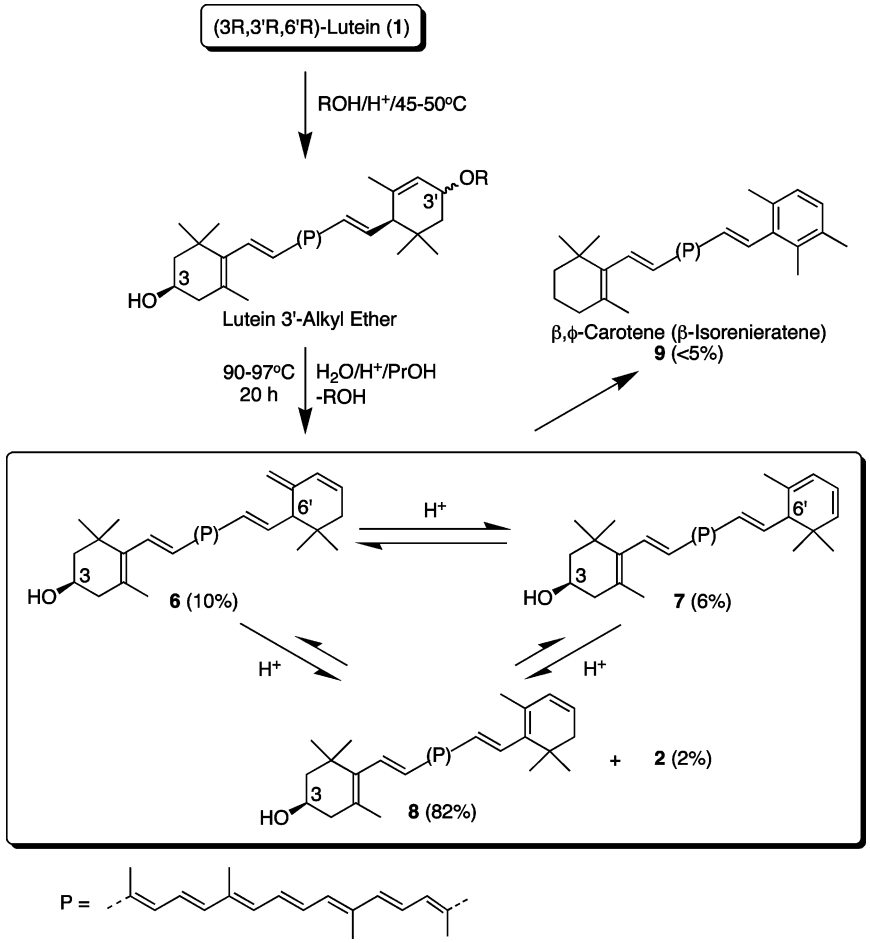
On the basis of our earlier results of the reductive deoxygenation of **1** with Et_3SiH/TFA, it was apparent that the ionic hydrogenation of **6**, **7**, and **8** would be the most practical route to **4**. Therefore, a two-step process was considered according to which **1** would be first dehydrated to a mixture of anhydroluteins (**6**−**8**) followed by ionic hydrogenation of these carotenoids with a much more effective hydride donor than Et_3SiH to provide **3** and **4**.

The first step of this transformation was accomplished with acid-catalyzed dehydration of **1** with a variety of mineral and organic acids, and the results are shown in Table 3 (Supporting Information). In all cases, **6** was the major product, and **7** and **8** were minor products. These results were also consistent with the one-pot reaction of **1** with Et_3SiH/TFA, in which these dehydration products were formed in about the same relative ratios prior to ionic hydrogenation.

Ionic hydrogenation of **8** would be expected to predominantly yield **4**, while **3** is presumably formed, to a greater extent, from **6** and **7**. Thus, the yield of **4** in the products of ionic hydrogenation of **6**−**8** could be increased at the expense of **3**, provided that the starting materials consisted of a much higher proportion of **8** relative to **6** and **7**.

To accomplish this objective, we conducted the acid-catalyzed dehydration of **1** at elevated temperatures in an attempt to isomerize **6** and **7** to the more thermodynamically stable **8** with an extended π-conjugation system. When the isomerization reactions were conducted in refluxing solutions of **1** in THF or TBME in the presence of mineral acids (HCl, H_2SO_4), only a partial conversion of **6** and **7** to **8** was observed; however, these reactions were also accompanied by considerable degradation and *E/Z*-isomerization. We proposed that the exposure of carotenoids to these harsh reaction conditions could be minimized if the isomerization were to be carried out in a heterogeneous system (solid−liquid phase) and in solvents in which **6**, **7**, and **8** would exhibit poor solubility. In this regard, the combination of an alcohol and H_2O was found to be most suitable. Therefore, the acid-catalyzed dehydration of **1** in refluxing solutions of alcohols such as ethanol, 1-propanol, or 2-propanol in the presence of H_2O was examined. The overall one-pot process for acid-catalyzed dehydration of **1** and isomerization of **6** and **7** to **8** is shown in Scheme 2.

Scheme 2. Acid-Catalyzed Dehydration of **1** (containing 6% of **2**) in 1-Propanol at High Temperature to **6**, **7**, and **8**[a]



[a] ROH = MeOH, EtOH, PrOH, or BuOH; H^+ = HCl or H_2SO_4 or H_3PO_4. *β,φ*-Carotene (isorenieratene, **9**), formed as a minor side product, is removed from the products by EtOH/hexane wash.

Initially, **1** was allowed to react with an alcohol, also used as solvent, in the presence of catalytic amounts of a mineral acid at 45−50 °C to give the corresponding lutein 3′-alkyl ether. This reaction has been routinely used for detection of allylic hydroxyl groups in these compounds.[36] The addition of H_2O at the beginning of this reaction was avoided because we had previously shown that, in the presence of water and catalytic amounts of acids, **1** undergoes epimerization at the 3′ position rather than dehydration.[24] Once **1** was completely converted to its 3′-alkyl ether, H_2O and additional acid were added, and the solution was heated under reflux to commence the elimination of alcohol and formation of a mixture of anhydroluteins (**6**−**8**). HPLC studies of the progress of this reaction revealed that at temperatures above 55 °C lutein 3′-alkyl ether gradually eliminated alcohol to form **6** as the major product and **7** and **8** as minor products. The isomerization of **6** and **7** to **8** proceeded rather slowly in refluxing solutions of ethanol (bp = 78 °C) and 2-propanol (bp = 82 °C) but was much more efficient at 90−97 °C in 1-propanol (bp = 97 °C). After 20 h in a refluxing solution of 1-propanol, the products were sequentially washed with ethanol and hexane to give a red crystalline mixture of **8** (82%), **6** (10%), **7** (6%), and **2** (2%). As noted earlier, approximately 6% of **2** was present in **1**, which, for the most part, remained unchanged throughout this process. HPLC analysis of the products revealed that even after 20 h of heating at 90−97 °C no significant *E*/*Z*-isomerization and/or degradation of carotenoids had taken place, and **6**−**8** were obtained in an overall yield of 86% from **1**. Approximately ≤5% of the *Z*-isomers of these carotenoids were formed by this process, and those were readily removed when the crystalline products were washed with ethanol and hexane. The ethanol/hexane fraction was also shown by HPLC to contain ≤5% of a hydrocarbon carotenoid that was identified from its NMR, MS, and UV−vis spectra as *β,φ*-carotene (*β*-isorenieratene, **9**) (Scheme 2). Compound **9** has been synthesized[37,38] and reported to occur in some species of photosynthetic brown bacteria (*Phaeobium*).[39] The formation of the aromatic end-group (*φ*-end group) in **9** may be explained by loss of a hydrogen atom (H-2′) from **8** to form an allylic free radical followed by the migration of a methyl radical from C-1′ to C-2′ and aromatization. However, deoxygenation of the hydroxyl group of **8** at C-3 that leads to the unsubstituted *β*-end group in **9** is not clearly understood and may proceed by an ionic and/or free radical mechanism. The ionic mechanism would involve protonation of the hydroxyl group and loss of water to form a carbocation intermediate that abstracts a hydride ion to form the product. The H-6′ in **6** and/or **7** is the most likely source of hydride ion because bisallylic hydrides have been shown to serve as H^- donors.[40] As noted earlier, the secondary hydroxyl groups in carotenoids **1**−**8** are generally found to be unreactive in ionic hydrogenation, and the minor quantities of **9** that are formed at high temperature (≥90 °C) in the presence of acids are indeed an exception.

When the dehydration of **1** was carried out for 4 h in refluxing EtOH according to Scheme 2, the final product consisted of a mixture of **8** (44%), **7** (23%), **6** (19%), and **2** (14%); **9** was not formed under these conditions. Increasing the reaction time, from 4 to 20 h, did not improve the yield of **8** relative to **6** and **7**. When the above mixture of **6**−**8** was refluxed in 2-propanol in the presence of acids, further isomerization of **6** and **7** to **8** could be promoted to yield these anhydroluteins in nearly the same ratios as those obtained in refluxing 2-propanol alone. This suggests that the acid-catalyzed isomerization of **6**−**8** proceeds via a thermody-

namically controlled equilibrium. However, this was not confirmed by subjecting the individually isolated anhydroluteins to acid-catalyzed isomerization.

In the second step of the transformation of **1** to **3** and **4**, the above mixtures of anhydroluteins **6**−**8** that were prepared in refluxing ethanol, or 1-propanol, were subjected to ionic reduction with TFA/$Me_3N{\cdot}BH_3$, and the results are summarized in Table 4 (Supporting Information). The quantitative distribution of the carotenoids in the products of these reactions was determined by HPLC. A nearly 2-fold increase in the relative composition of **8** from 44% to 82% in the starting materials of these reactions resulted in about a 2-fold increase in the ratio of **4** to **3** in the products. This finding and the fact that **3** was not isomerized to **4** under the reaction conditions suggest that **4** is exclusively formed from **8**, although this has not been unequivocally confirmed by subjecting a pure sample of this carotenoid to ionic reduction. Unlike the deoxygenation of **1** with TFA/Et_3SiH, the ionic reduction of **6**−**8** with TFA/$Me_3N{\cdot}BH_3$ produced **3** and **4** in a crude yield of 85% as mainly *all-E* and was not accompanied by any significant *E/Z*-isomerization and/or degradation. After removal of **2** and the unreacted **6**−**8** by column chromatography, a mixture of **4** (76%), **3** (23%), and **5** (1%) was obtained in 80% isolated yield.

The combination of TFA with other amine-boranes such as $Me_2NH{\cdot}BH_3$ or $Me_3CNH_2{\cdot}BH_3$ proved to be as effective as $Me_3N{\cdot}BH_3$ and readily transformed **6**−**8** to **3** and **4** in similar yields. The crystallized product obtained from this reaction can be safely used as a nutritional supplement without further purification by column chromatography. This is because the unreacted **6** and **7** as well as minor quantities of **2** that are present in the products are of dietary origin and are routinely found in the human plasma and tissues.[3−7,29] Although **8** has not been isolated from foods or human plasma, the 3′,4′-didehydro end-group of this carotenoid is identical to that of vitamin A_2; therefore this structural modification would not be expected to adversely affect the biological properties of this carotenoid. We have also shown that the need for column chromatography can be omitted by a second crystallization of the products, which results in substantial removal of **2** as well as **6**−**8** without affecting the relative composition of **3** and **4**.

In summary, this report describes an efficient method for allylic deoxygenation of **1** with TFA and a wide range of hydride donors to arrive at optically active **3** in ≥90% isolated yield under mild reaction conditions.[41] In a two-step process, the acid-catalyzed dehydration of **1** at high temperature affords a mixture of **6**−**8** in which **8** is the major product. The ionic hydrogenation of this mixture followed by crystallization and column chromatography yields a mixture of **3** (23%), **4** (76%), and **5** (1%) in an overall isolated yield of 69%.[42]

Experimental Section

General Experimental Procedures. Commercially available (3*R*,3′*R*,6′*R*)-lutein (**1**, 85% pure, Kemin Health, Des Moines, IA) is isolated from marigold flowers and contains approximately 6% (3*R*,3′*R*)-zeaxanthin (**2**). This carotenoid and all other reagents as well as HPLC grade solvents were used without further purification.

HPLC analyses were performed on an Agilent Technology Model 1100 HPLC system equipped with a quaternary solvent delivery system, 1100 autosampler, thermostated column compartment, and 1100 diode array detector. Details regarding analytical and semipreparative HPLC separations are described in the Supporting Information.

Mass spectra of carotenoids were obtained by FAB on a JEOL SX102a mass spectrometer. The matrix was magic bullet, consisting of a 5:1 mixture of dithiothreitol/dithioerythritol. Employing this technique, the parent molecular ions of carotenoids appeared as radical cations and not as $(M + H)^+$ ions. ^{1}H NMR (400 MHz or 500.13 MHz) and ^{13}C NMR (100 or 125.76 MHz) spectra were recorded on a Bruker AV-400 (automated) or DRX-500 spectrometer. Chemical shifts of protons were referenced to the residual proton solvent signal of $CDCl_3$ at 7.27 ppm. Chemical shifts of carbons in ^{13}C NMR spectra were referenced to the chemical shift of $CDCl_3$ at 77.0 ppm. Other NMR experiments performed on the DRX-500 spectrometer were DEPT-135, HSQC, DQF-COSY, and HMBC. The UV/visible absorption spectra were obtained by HPLC-photodiode array detection between 200 and 600 nm at the rate of 12 spectra per minute; the UV/visible spectra of the isolated carotenoids were also obtained in single solvents on a Beckman UV/visible spectrophotometer Model DU-530. Circular dichroism (CD) spectra were obtained on a JASCO (Model J810) instrument. A mixture of hexane, ether, and methanol (10:3:1) was used as the background solvent.

Deoxygenation of Lutein (1) with Et_3SiH/TFA. A solution of **1** (0.300 g, 85% pure 0.255 g, 0.448 mmol) in CH_2Cl_2 (25 mL) was first treated with Et_3SiH (0.150 mL, 0.109 g, 0.94 mmol) followed by TFA (0.12 mL, 0.178 g, 1.56 mmol). The mixture was stirred at ambient temperature under an atmosphere of nitrogen, and the course of the reaction was followed by HPLC (eluent A). After 8 h, the product was treated with 5% aqueous $NaHCO_3$ (15 mL). The organic layer was removed, washed with water (3 × 15 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in acetone to remove the non-carotenoid impurities and filtered. Acetone was evaporated, and the residue was crystallized from ethanol (4 mL) at 0 °C. The product was dried under high vacuum to give 0.223 g of an orange solid, which was shown by HPLC (eluent A) to consist of a mixture of carotenoids. These were separated by semipreparative HPLC (eluent B) and identified from their UV−visible, mass, and NMR spectra as **2** (14%), **3** (25.2%), **4** (39.1%), **5** (3%), and anhydroluteins **6**−**8** (18.7%).

(3*R*,3′*R*)-Zeaxanthin (2): UV−visible, mass, and NMR (400 MHz) spectra were consistent with published data.[31,43]

(3*R*,6′*R*)-α-Cryptoxanthin (3): mp 172−174 °C, UV/visible (hexane) λ_{max} (444 main max), 473 nm; CD (hexane/ether/MeOH, 10:3:1) 239 (+2.83), 271 (0), 282 (−1.30), 300 (0), 333 nm (+0.80); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 and 0.91 (s, Me-16′ or Me-17′), 1.08 (s, Me-16, Me-17), 1.20 (br m, H-2′β), 1.46 (m, H-2′α), 1.48 (m, H-2β), 1.59 (d, J = 1.8 Hz, Me-18′), 1.75 (s, Me-18), 1.77 (ddq, J = 12.0, 2.8, 2.1 Hz, H-2α), 1.92 (s, Me-19′), 1.97 (s, Me-19, Me-20, Me-20′), 2.02 (br, H-3′), 2.04 (dd, J = 16.6, 10.0 Hz, H-4β), 2.18 (d, J = 9.3 Hz, H-6′), 2.39 (br dd, J = 16.6, 4.3 Hz, H-4α), 4.01 (m, H-3), 5.42 (br, H-4′), 5.54 (dd, J = 15.3, 9.3 Hz, H-7′), 6.10 (d, J = 12.0 Hz, H-10′), 6.11 (d, J = 15.5 Hz, H-7), 6.12 (d, J = 15.3 Hz, H-8′), 6.15 (d, J = 15.5 Hz, H-8), 6.16 (d, J = 12.0 Hz, H-10), 6.25 (br m, H-14, H-14′), 6.34 (d, J = 15.0 Hz, H-12), 6.37 (d, J = 15.0 Hz, H-12′), ∼6.63 (br dd, $J \approx$ 15, 12 Hz, H-11, H-11′, H-15, H-15′). Assignments for signals due to Me-16′ and Me-17′ may be interchanged. The ^{1}H data were in agreement with literature values of the optically inactive compound.[18] The NMR data of **3** would be expected to be the same as that of the optically inactive compound due to the location of the chiral centers on the far side end-groups of this carotenoid. ^{13}C NMR ($CDCl_3$, 100 MHz): 12.8 (Me-19, Me-20, Me-20′), 13.1 (Me-19′), 21.6 (Me-18), 23.0 (Me-18′), 23.1 (C-3′), 27.0 & 27.7 (Me-16′ or Me-17′), 28.7 and 30.3 (Me-16 or Me-17), 31.7 (C-2′), 32.5 (C-1′), 37.1 (C-1), 42.6 (C-4), 48.4 (C-2), 54.9 (C-6′), 65.1 (C-3), 120.8 (C-4′), 124.8 & 125.0 (C-11 or C-11′), 125.5 (C-7), 126.1 (C-5), 129.9 (C-15′), 130.1 (C-15), 130.2 (C-10′), 131.1 (C-7′), 131.3 (C-10), 132.3 (C-14′), 132.6 (C-14), 134.5 (C-5′), 135.6 (C-9′), 135.7 (C-9), 136.2 (C-8′), 136.4 (C-13′), 136.6 (C-13), 137.1 (C-12′), 137.6 (C-12), 137.8 (C-6), and 138.5 (C-8). Assignments for signals due to C-11 and C-11′, Me-16 and Me-17, and Me-16′ and Me-17′ may be interchanged. The proton and carbon NMR chemical shifts of **3** were also in agreement with those of the published values for the end-groups and the polyene chain of carotenoids.[31] FABMS molecular radical cation at *m*/*z* 552.41 (100%) (calculated for $C_{40}H_{56}O$, *m*/*z* 552.88).

(3*R*)-β-Cryptoxanthin (4): mp 134−136 °C (dec); UV/visible (hexane) λ_{max} (452 main maximum), 477 nm; CD (hexane/ether/MeOH, 10:3:1) 243 (+1.50), 264 (0), 283 (−1.80), 311 (0), 349 nm (+0.67); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, Me-16′, Me-17′), 1.08 (s, Me-16, Me-17), 1.46 (m, H-2′), 1.48 (m, H-2β), 1.62 (m, H-3), 1.76 (s, Me-18′), 1.78 (s, Me-18), 1.77 (m, H-2α), 1.98 (s, Me-19, Me-20, Me-19′, Me-20′), 2.02 (m, H-4′), 2.04 (m, H-4β), 2.39 (br dd, J = 16.6, 4.3 Hz, H-4α), 4.01 (m, H-3), 6.10−6.20 (unresolved m, H-7, H-7′, H-8, H-8′, H-10, H-10′), 6.26 (br m, H-14, H-14′), 6.36 (d, J = 15.0 Hz, H-12′), 6.37 (d, J = 15.0 Hz, H-12), ∼6.63 (br dd, $J \approx$ 15, 12 Hz, H-11, H-11′, H-15, H-15′); the ^{1}H data were in agreement with literature values of the optically inactive compound;[18] ^{13}C NMR ($CDCl_3$, 100 MHz) 12.8 (Me-19, Me-20, Me-19′, Me-20′), 19.3 (C-3′), 21.6 (Me-18), 21.8 (Me-18′), 28.7 (Me-17), 29.0 (Me-16′, Me-17′), 30.3 (Me-16), 33.1 (C-4′), 34.3 (C-1′), 37.1 (C-1), 39.7 (C-2′), 42.6 (C-4), 48.5

(C-2), 65.1 (C-3), 124.9 (C-11), 125.1 (C-11′), 125.6 (C-7), 126.2 (C-5), 126.7 (C-7′), 129.4 (C-5′), 129.9 (C-15′), 130.1 (C-15), 130.8 (C-10′), 131.3 (C-10), 132.4 (C-14′), 132.7 (C-14), 135.6 (C-9), 136.1 (C-9′), 136.4 (C-13′), 136.6 (C-13), 137.2 (C-12′), 137.6 (C-12), 137.8 (C-8′), 137.9 (C-6, C-6′) and 138.5 (C-8). Assignments for signals due to Me-16′ and Me-17′ may be interchanged. The proton and carbon NMR chemical shifts of **3** were also in agreement with those of the published values for the end-groups and the polyene chain of carotenoids.[31] FABMS molecular radical cation at *m*/*z* 552.40 (100%) (calculated for $C_{40}H_{56}O$, *m*/*z* 552.88).

(3*R*,5′*RS*,6′*R*)-3′,4′-Didehydro-5′,6′-dihydro-β,β-caroten-3-ol (5): UV/visible (hexane) λ_{max} (446 main maximum), 472 nm; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 & 0.98 (s, Me-16′ or Me-17′), 0.86 (d, J = 7.7 Hz, Me-18′), 1.08 (s, Me-16, Me-17), 1.49 (t, J = 12.0 Hz, H-2β), 1.65 (br dd, $J \sim$ 16.0 Hz, H-2′β), 1.75 (s, Me-18), 1.78 (ddq, J = 12, 2.8, 2.1 Hz, H-2α), 1.87 (dd, J = 10.0, 5.3 Hz, H-6′), 1.93 (dd, J = 16.0, 5.0 Hz, H-2′α), 1.98 (s, Me-19, Me-19′, Me-20, Me-20′), 2.05 (dd, J = 16.5, 10.0 Hz, H-4β), 2.39 (br dd, J = 16.5, 5.0 Hz, H-4α), 2.51 (br, H-5′), 4.03 (m, H-3), 5.42 (br, H-4′), 5.45 (dd, J = 15.5, 10.0 Hz, H-7′), 5.61 (m, H-3′), 6.10 (d, J = 12.0 Hz, H-10′), 6.11 (d, J = 15.5 Hz, H-7), 6.12 (d, J = 15.5 Hz, H-8′), 6.15 (d, J = 15.5 Hz, H-8), 6.16 (d, J = 12.0 Hz, H-10), 6.25 (br m, H-14, H-14′), 6.34 (d, J = 14.6 Hz, H-12′), 6.37 (d, J = 14.6 Hz, H-12), 6.63 (br dd, $J \approx$ 15, 12 Hz, H-11, H-11′, H-15, H-15′); assignments for signals due to Me-16′ and Me-17′ may be interchanged; ^{13}C NMR ($CDCl_3$, 125.76 MHz) 12.8 (Me-19, Me-20, Me-20′), 13.2 (Me-19′), 19.3 (Me-18′), 21.6 (Me-18), 27.5 and 29.8 (Me-16′ or Me-17′), 28.7 and 30.3 (Me-16 or Me-17), 30.8 (C-5′), 32.9 (C-1′), 36.0 (C-2′), 37.1 (C-1), 42.6 (C-4), 48.5 (C-2), 53.8 (C-6′), 65.1 (C-3), 124.8 (C-3′), 125.1 (C-11, C-11′), 125.5 (C-7), 126.2 (C-5), 129.6 (C-10′), 129.8 (C-4′), 129.9 (C-15′), 130.1 (C-15), 130.7 (C-7′), 131.3 (C-10), 132.2 (C-14′), 132.6 (C-14), 135.6 (C-9′), 135.8 (C-9), 136.3 (C-13′), 136.6 (C-13), 137.0 (C-8′), 137.4 (C-12′), 137.6 (C-12), 137.8 (C-6), and 138.5 (C-8). Assignments for signals due to Me-16 and Me-17 as well as Me-16′ and Me-17′ may be interchanged. FABMS molecular radical cation at *m*/*z* 552.50 (100%) (calculated for $C_{40}H_{56}O$, *m*/*z* 552.88).

Anhydroluteins (6−8). The UV−visible, mass, and NMR spectra of **6**, **7**, and **8** were identical with those of authentic samples of these carotenoids that were synthesized according to our published method.[29]

Deoxygenation of Lutein (1) to α-Cryptoxanthin (3) with $Me_3N{\cdot}BH_3$/TFA. To a solution of **1** (0.300 g, 85% pure 0.255 g, 0.448 mmol) in CH_2Cl_2 (20 mL) was added $Me_3N{\cdot}BH_3$ (45.8 mg, 0.628 mmol), and the mixture was cooled to 0 °C under nitrogen. TFA (0.14 mL, 0.207 g, 1.82 mmol) was added, and the mixture was stirred at 0 °C for 1.5 h. The product was sequentially washed with water (20 mL), aqueous $NaHCO_3$ (20 mL, 5%), and water (20 mL) and dried over Na_2SO_4. After solvent evaporation under reduced pressure, the residue was crystallized from acetone and ethanol at −15 °C to give a red solid, which was dried under high vacuum at ambient temperature overnight and identified as **3** (0.232 g, 0.42 mmol; 94%) from its UV−visible, MS, ^{1}H NMR, and CD spectra.

Deoxygenation of Lutein (1) to α-Cryptoxanthin (3) with ZnI_2/$NaCNBH_3$. A solution of **1** (0.300 g, 85% pure 0.255 g, 0.448 mmol) in CH_2Cl_2 (20 mL) was treated with $NaCNBH_3$ (0.211 g, 3.36 mmol) and ZnI_2 (0.575 g, 1.80 mmol). The mixture was stirred at ambient temperature under N_2, and the course of the reaction was followed by HPLC (eluent A) and TLC (hexane/acetone, 4:1; lutein (R_f = 0.18), α-cryptoxanthin (R_f = 0.51)). After 1 h, the product was filtered through Celite, and the solvent was evaporated under reduced pressure. The residue was crystallized from acetone and ethanol at −15 °C to give an orange solid, which was dried under high vacuum at ambient temperature overnight and identified as **3** (0.223 g, 0.404 mmol; 90%) from its UV−visible, MS, and ^{1}H NMR spectra.

Deoxygenation of Lutein (1) to α-Cryptoxanthin (3) with $ZnBr_2$/$Na[BH_3(OCOCF_3)]$. TFA (0.14 mL, 0.207 g, 1.82 mmol) was added dropwise to a suspension of $NaBH_4$ (72 mg, 1.90 mmol) in THF (2 mL) cooled to 10−15 °C under N_2. The mixture was stirred at room temperature for 10 min to give a clear solution. $ZnBr_2$ (0.130 g, 0.577 mmol) was added to a solution of **1** (0.300 g, 85% pure 0.255 g, 0.448 mmol) in CH_2Cl_2 (20 mL) at 0 °C under N_2. The above solution of $Na[BH_3(OCOCF_3)]$ (1.82 mmol) was added to the mixture at 0−5 °C, and the course of the reaction was followed by HPLC (eluent A) and TLC (hexane/acetone, 4/1; **1** (R_f = 0.18), **3** (R_f = 0.51)). After 5 h, the product was treated with aqueous $NaHCO_3$ (10 mL, 5%) and allowed to stir at ambient temperature for 10 min. The organic layer was removed, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from acetone and ethanol at −15 °C to give an orange solid, which was dried under high vacuum at ambient temperature overnight and identified as **3** (0.23 g, 0.417 mmol; 93%) from its UV−visible, MS, ^{1}H NMR, and CD spectra.

Two-Step Transformation of 1 into 3 and 4. Step 1: Acid-Catalyzed Dehydration of Lutein (1) at High Temperature. A suspension of **1** (1.0 g, 85% pure 0.85 g, 1.49 mmol) in 30 mL of 1-propanol was treated with 0.2 mL of 50% aqueous H_2SO_4 (v/v), and the mixture was heated at 50 °C for 1 h until a dark red solution was obtained and **1** was completely converted to lutein 3′-propyl ether. Water (40 mL) was added followed by 0.4 mL of 50% aqueous H_2SO_4 (v/v), and the mixture was heated to 90 °C. The course of the acid-catalyzed isomerization of anhydroluteins **6** and **7** to **8** was followed by HPLC (eluent A). After 20 h, the mixture was allowed to cool to room temperature, H_2O (10 mL) was added, and the red crystals were filtered and sequentially washed with ethanol (15 mL) and hexane (15 mL) and dried under high vacuum at ambient temperature. The filtrate was saved for HPLC analysis and identification of carotenoids. The red crystalline product (0.85 g, 85% pure, 0.72 g) was shown by HPLC (eluent A) to consist of a mixture of **2** (2%, 0.014 g), **6** (10%, 0.072 g), **7** (6%, 0.043), and **8** (82%, 0.590 g) [0.705 g total anhydroluteins **6**−**8**, 1.28 mmol, 86%]. A small quantity of this crude product was subjected to semipreparative HPLC (eluent B), and the individually isolated **6**, **7**, and **8** were identified by comparison of their UV−visible, mass, and NMR spectra with those of authentic samples.[29] The crude crystalline product from this reaction was used in a subsequent reaction with $Me_3N{\cdot}BH_3$/TFA (step 2) without further purification. The filtrate from above was shown by HPLC to consist of mainly *cis*-isomers of **6**, **7**, and **8** as well as a carotenoid, which was separated by semipreparative HPLC and identified from its UV−visible, mass, and NMR spectra as **9** (<5%).

β,ϕ-Carotene (9): UV/visible (hexane) λ_{max} (452 main maximum), 477 nm; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, Me-16, Me-17), 1.46 (m, H-2), 1.62 (m, H-3), 1.73 (s, Me-18), 1.99 (s, Me-19, Me-20), 2.00 (s, Me-20′), 2.04 (m, H-4), 2.09 (s, Me-19′), 2.24 (s, C1′-Me), 2.28 and 2.29 (s, C2′-Me and C5′-Me), 6.13−6.25 (unresolved m, H-7, H-8, H-8′, H-10, H-10′), 6.27 (unresolved m, H-14, H-14′), 6.28 (unresolved, H-7′), 6.33 (d, J = 15.0 Hz, H-12), 6.41 (d, J = 15.0 Hz, H-12′), ∼6.58−6.68 (unresolved m, H-11, H-11′, H-15, H-15′), 6.97 (s, H-3′ and H-4′); ^{1}H NMR data were in agreement with the literature values;[38] ^{13}C NMR ($CDCl_3$, 100 MHz) 12.8 (Me-19, Me-20, Me-19′, Me-20′), 17.1 (Me-16′), 19.3 (C-3), 20.5 (Me-17′), 21.0 (Me-18′), 21.8 (Me-18), 29.0 (Me-16, Me-17), 33.1 (C-4), 34.3 (C-1), 39.6 (C-2), 124.7 (C-11′), 125.2 (C-11), 126.4 (C-4′, C-7′), 126.7 (C-7), 127.2 (C-3′), 129.4 (C-5), 129.9 (C-15), 130.3 (C-15′), 130.9 (C-10), 132.2 (C-10′), 132.4 (C-14, C-14′), 132.9 (C-5′), 133.6 (C-1′), 134.2 (C-2′), 135.4 (C-9′), 136.1 (C-9), 136.3 (C-13), 136.7 (C-13′), 137.2 (C-12, C-12′), 137.8 (C-8), 137.9 (C-6), 138.1 (C-6′) and 130.0 (C-8′). Assignments for signals due to Me-17′ and Me-18′, C-3′ and C-4′, C-15 and C-15′, and C-1′ and C-2′, may be interchanged. The proton and carbon NMR chemical shifts of **3** were also in agreement with those of the published values for the end-groups and the polyene chain of carotenoids.[31] FABMS molecular radical cation at *m*/*z* 532.2 (100%) (calculated for $C_{40}H_{52}$, *m*/*z* 532.85).

Step 2: Ionic Hydrogenation of Anhydroluteins (6−8) to 3 and 4 with $Me_3N{\cdot}BH_3$/TFA. The crude product prepared in step 1 (0.85 g, 85% pure) that consisted of a mixture of **2** (0.014 g) and anhydroluteins **6**−**8** (0.705 g, 1.28 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with $Me_3N{\cdot}BH_3$ (0.114 g, 1.56 mmol). TFA (0.36 mL, 0.533 g, 4.67 mmol) was added at ambient temperature, and the course of the reaction was followed by HPLC (eluent A). After 3 h, the product was sequentially washed with H_2O (20 mL), 5% $NaHCO_3$ (20 mL), and H_2O (20 mL). The organic layer was removed, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from acetone and ethanol at −15 °C to give an orange solid (0.68 g), which was dried under high vacuum at ambient temperature overnight. The product was shown by HPLC (eluent A) to consist of a mixture of **3** (18%), **4** (61%), **5** (1%), and unreacted **2** (4%) as well as anhydroluteins **7** (9%) and **8** (7%). The solid was further purified by flash column chromatography on silica gel (hexane:acetone, 19:1) to yield a mixture of **3** (23%), **4** (76%), and **5** (1%) [0.57 g total cryptoxanthins **3**−**5**, 1.03 mmol, 80%]. To avoid column chromatography, the crude product was purified by two consecutive crystallizations to yield a mixture of **3** (21%), **4** (72%), **7** (4%), and **8** (3%). The identity

of these carotenoids was established from the UV−visible, MS, and ^{1}H NMR spectra of the individually isolated compounds.

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Supporting Information Available: Details regarding analytical and semipreparative HPLC separations and Tables 1−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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