Partial Synthesis and Structural Elucidation of the Oxidative Metabolites of Lycopene Identified in Tomato Paste, Tomato Juice, and Human Serum

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Two oxidative metabolites of lycopene in tomato paste, tomato juice, and human serum have been prepared by partial synthesis from oxidation of lycopene with *m*-chloroperbenzoic acid (MCPBA) followed by acidic hydrolysis. Extensive ^{1}H and ^{13}C NMR spectroscopy studies of the purified products of these reactions have confirmed that the major oxidation products of lycopene (**I**) are lycopene 1,2-epoxide (**II**) and lycopene 5,6-epoxide (**III**) (tentative assignment). Several diepoxides of lycopene, namely, lycopene 1,2;5,6-diepoxide (**IV**), lycopene 1,2;5′,6′-diepoxide (**V**), lycopene 5,6;5′,6′-diepoxide (**VI**), and lycopene 1,2;1′,2′-diepoxide (**VII**), which were formed as minor products, were tentatively identified. Whereas lycopene 1,2-epoxide was found to be fairly stable, lycopene 5,6-epoxide underwent cyclization to form a mixture of diastereomeric epoxides A (**VIII**, major) and B (**IX**, minor). The trivial names of 2,6-cyclolycopene-1,5-epoxides A (**VIII**) and B (**IX**) have been assigned to these compounds with a novel five-membered ring end-group. Hydrolysis of **VIII** and **IX** in dilute solutions of sulfuric acid gave an epimeric mixture of 2,6-cyclolycopene-1,5-diols A (**X**, major) and B (**XI**, minor). During chromatographic purification on n-silica gel, **II** and **III** partially cyclized to 1,16-didehydro-2,6-cyclolycopen-5-ol (**XII**) and epoxides **VIII** and **IX** partially converted to their respective diols, **X** and **XI**. In the course of isolation and purification, the oxidation products of lycopene with MCPBA were found to be extremely sensitive to chromatography on n-silica gel and underwent rearrangement to a number of cyclic epoxides and diols. Upon acid treatment of the mixture of lycopene epoxides, a bicyclic diepoxide of lycopene was formed, which was identified as lycopene 1,6;2,5-diepoxide (**XIII**). Diols **X** and **XI** have also been detected at low concentrations in tomato paste, tomato juice, and human serum. All synthetic compounds have been fully characterized by NMR, UV−vis, and MS.

Keywords: *1,16-Didehydro-2,6-cyclolycopen-5-ol; 2,6-cyclolycopene-1,5-diol; 2,6-cyclolycopene-1,5-epoxide; lycopene 1,6;2,5-diepoxide; lycopene 5,6-epoxide; lycopene oxidation products; new serum carotenoids; carotenoid metabolites; NMR; HPLC/mass spectrometry*

INTRODUCTION

ψ,*ψ*-Carotene (lycopene), the major red pigment in tomatoes and tomato-based food products (Tonucci et al., 1995), is also one of the most abundant non-vitamin A active carotenoids found at relatively high concentrations in human plasma and breastmilk of lactating mothers (Khachik et al., 1992a, 1997a). The biological importance and nutritional significance of lycopene in humans have been the subject of intense research during the past several years (Stahl and Sies, 1996). For example, in a recent prospective cohort epidemiological study, the high consumption of lycopene-rich tomato-based food products has been associated with a reduction of the risk of prostate cancer (Giovannucci et al., 1995). In another study, the inhibitory effects of dietary carotenoids such as *β*,*ε*-carotene (α-carotene), *β*,*β*-carotene (*β*-carotene), lycopene, and (3*R*,3′*R*,6′*R*)-*β*,*ε*-carotene-3,3′-diol (lutein) on the prevention of colon cancer in rats was investigated, and it was concluded that lycopene and lutein given to rats in small doses may potentially prevent colon carcinogenesis (Narisawa et al., 1996). More recently, in a number of in vitro studies, we have reported on biological activity of lycopene and particularly its recently identified oxidative metabolites, 2,6-cyclolycopene-1,5-diols A and B; this has been one of the motivating factors behind the work presented here (King et al., 1997).

For the first time in 1992, we tentatively identified an oxidation product of lycopene, namely lycopene 5,6-diol, in human plasma (Khachik et al., 1992a) and tomato paste (Khachik et al., 1992b). This compound was later shown to be also present in many tomato-based food products (Tonucci et al., 1995). In 1995, we proposed a possible pathway for the oxidation of lycopene and the formation of an oxidative metabolite of this potentially useful cancer preventive agent in humans (Khachik et al., 1995). In all of these publications, the identification of the lycopene metabolite was solely

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based on comparison of the high-performance liquid chromatography-UV−visible/mass spectrometry (HPLC-UV−vis/MS) profile of this compound with that of a sample of lycopene-5,6-diol, prepared by partial synthesis according to the procedures of Bush and Zechmeister (1958) and Ritacco et al. (1984). However, on the basis of extensive nuclear magnetic resonance (NMR) spectroscopy data of the oxidation products of lycopene prepared by partial synthesis, we have now determined that the original structure proposed for lycopene-5,6-diol by Bush and Zechmeister (1958), Ritacco et al. (1984), and ourselves was incorrectly assigned.

In this paper we present a convenient method for the partial synthesis of several oxidation products of lycopene and their acidic hydrolysis reactions, which ultimately lead to the formation of a number of hydroxycyclolycopenes with novel five-membered ring endgroups. Employing ^{1}H and ^{13}C NMR spectroscopy, HPLC-UV−vis/MS, we have fully characterized several of the oxidative metabolites of lycopene and have established the correct structures and relative, but not absolute, stereochemistries of two metabolites of this dietary carotenoid in tomato-based food products and human serum. To search for the source and natural occurrence of the oxidation products of lycopene, extracts from tomato paste and tomato juice have also been extensively examined by HPLC-UV−vis/MS. On the basis of the comparative carotenoid profiles of these foods and human plasma, in this paper we propose possible metabolic transformations that may explain the presence of the oxidative metabolites of lycopene in humans.

EXPERIMENTAL PROCEDURES

Apparatus. A Beckman model 114M ternary solvent delivery system equipped with a Beckman model 421 controller was interfaced into a Hewlett-Packard (HP) 1040A rapid-scanning UV−vis photodiode array detector. The data were stored and processed by an HP 9000/Series 300 (Chem-Station) computing system, in combination with an HP model 9153B disk drive, color display monitor, model 35741, and a model 7470A plotter. The absorption spectra of the carotenoids were recorded between 200 and 600 nm at a rate of 12 spectra/min. This HPLC system was interfaced into a Hewlett-Packard model 5989A particle beam mass spectrometer. Eluate from the HPLC was divided with a ratio of 1:3, with the lesser amount entering the particle beam interface, which was operated at a desolvation temperature of 45 °C. Electron capture negative ionization (ECNI) was achieved using methane at a pressure of 0.85 Torr and a source temperature of 250 °C. Spectra were collected from *m*/*z* 100 to 700 using a scan cycle time of 1.5 s.

Chromatographic Procedures. The analytical reversed-phase and normal-phase separations were carried out by employing eluents A and B, respectively, whereas normal-phase semipreparative separations were carried out with eluents C and D. Chromatographic analysis with all of the eluents were simultaneously monitored at 470- and 456-nm wavelengths. The column flow rate with all of the eluents in analytical separations was 0.70 mL/min.

Reversed-Phase Separations (Eluent A). These separations employed a Microsorb (25-cm length × 4.6-mm i.d.) C_{18} (5-μm spherical particles) column (Rainin Instrument Co., Wouburn, MA), which was protected with a Brownlee guard cartridge (3-cm length × 4.6-mm i.d.) packed with Spheri-5-C_{18} (5-μm particle size). Eluent A consisted of an isocratic mixture of acetonitrile (85%), methanol (10%), dichloromethane (2.5%), hexane (2.5%), and *N*,*N*-diisopropylethylamine (DIPEA, 0.1%) at time 0, followed by a linear gradient beginning at 10 min and completed at 40 min. The final composition of the gradient mixture was acetonitrile (45%), dichloromethane (22.5%), hexane (22.5%), methanol (10%), and DIPEA (0.1%). At the end of the gradient, the column was re-equilibrated for 15 min under the initial isocratic conditions. The HPLC injection solvent was a mixture of acetonitrile (40%), methanol (20%), dichloromethane (20%), hexane (20%), and DIPEA (0.1%).

Normal-Phase Separations (Eluent B). These separations were carried out on a silica-based nitrile-bonded (25-cm length × 4.6-mm i.d.; 5-μm spherical particle) column (Regis Chemical Co., Morton Grove, IL), which was protected with a Brownlee nitrile-bonded guard cartridge (3-cm length × 4.6 mm i.d.; 5-μm particle size). For this separation a linear gradient with a two-pump solvent module was used. An isocratic mixture of hexane (93%) and dichloromethane (7%) containing 0.1% of DIPEA was pumped for the first 20 min. This was followed at time 20 by a linear gradient for 15 min during which the composition of hexane was reduced to 40% and the composition of dichloromethane/0.1% DIPEA was increased to 60%. At the end of the gradient, the column was equilibrated under the initial isocratic conditions for 15 min. The HPLC injection solvent with all of the analytical and semipreparative normal-phase separations was a mixture of hexane (90%), dichloromethane (10%), and DIPEA (0.1%).

Semipreparative Normal-Phase Separations. These separations were carried out on a semipreparative silica-based nitrile-bonded (25-cm length × 10.0-mm i.d.; 5-μm spherical particle) column (Regis Chemical Co.), which was protected with a Brownlee nitrile-bonded guard cartridge (3-cm length × 4.6 mm i.d.; 5-μm particle size). Eluents C−E at a flow rate of 4.3 mL/min were employed with this column.

Eluent C consisted of an isocratic mixture of hexane (95%), dichloromethane (5%), and DIPEA (0.1%).

Eluent D consisted of an isocratic mixture of hexane (95%), dichloromethane (5%), methanol (0.1%), and DIPEA (0.1%).

Eluent E consisted of an isocratic mixture of hexane (75%), dichloromethane (25%), methanol (0.25%), and DIPEA (0.10%).

UV−Vis Spectrophotometry and NMR Spectroscopy. Absorption spectra of the carotenoids in various solvents were recorded on a Beckman DU-7 UV−vis spectrophotometer.

The ^{1}H NMR (400.13 and 500.13 MHz) and ^{13}C NMR (100.62 and 125.76 MHz) spectra were acquired on Bruker DRX-400 and DRX-500 spectrometers. The spectra for compounds **II**, **VII**−**IX**, **XII**, and **XIII** were measured in benzene-d_6 (99.80% D) and those of compounds **X** and **XI** in $CDCl_3$ (99.95% D quality), which was purified over Al_2O_3 before use. Chemical shifts of protons and carbon-13 are related to the residual solvent signals of benzene-d_6 (7.15 ppm in ^{1}H, 128.00 ppm in ^{13}C) and $CDCl_3$ (7.26 ppm in ^{1}H, 77.0 ppm in ^{13}C). Other NMR experiments performed were H,H−COSY (homonuclear chemical shift correlated 2D spectroscopy), T-ROESY (rotating frame nuclear Overhauser effect spectroscopy), DEPT-135 (distortionless enhancement by polarization transfer), and inverse HMQC (hetero multiple quantum coherence spectroscopy). The application of modern NMR techniques for structural elucidation of carotenoids has been described in detail by Englert et al. (1993, 1995). The multiplicities of the signals have been abbreviated as s (singlet), d (doublet), m (multiplet), n (narrow), and b (broad).

Reagents and Materials. Large quantities (20 g) of purified *all-E*-lycopene were donated by LycoRed Natural Products Industries (Beer Sheva, Israel). This sample was found by spectrophotometric analysis, HPLC-UV−vis/MS and ^{1}H NMR to be ∼96% pure lycopene. Although the NMR spectrum of this sample did not show the presence of any *Z* isomers, HPLC analysis revealed the presence of 95% pure *all-E* and 5% 5-*Z*-lycopene. For this purpose, the HPLC methods used was that of Hengartner et al. (1992), which employs two normal-phase Nucleosil columns in series to separate 13 mono-*Z* and di-*Z*-isomers of *all-E*-lycopene. *m*-Chloroperoxybenzoic acid (MCPBA), *N*,*N*-diisopropylethylamine (DIPEA), and triethylamine were obtained from Aldrich Chemical Co. n-Silica gel (60−200 mesh) for flash column chromatography was purchased from J. T. Baker. HPLC solvents, acetonitrile, dichloromethane, hexane, and methanol

(Fisher Scientific Products) were used without purification. One unit of human serum (220 mL) was obtained from the American Red Cross (Baltimore, MD).

Extraction of Tomato Paste and Tomato Juice. Canned tomato juice and paste were purchased from a local supermarket and were extracted according to our earlier published procedures with the exception that DIPEA (2% v/w of sample) was added at the beginning of the extraction (Khachik et al., 1992b; Tonucci et al., 1995) and to all organic solvents used throughout sample preparation. For example, the extracted tomato paste (40 g) was dissolved in 100 mL of dichloromethane (0.1% DIPEA), and 1 mL aliquots were evaporated to dryness and redissolved in 1 mL of the appropriate injection solvents for quantitative and qualitative identification of the lycopene metabolites by reversed-phase (eluent A) and normal-phase (eluent B) HPLC.

Extraction and Isolation of Lycopene Metabolites from Human Serum. Human serum was extracted according to our published procedure (Khachik et al., 1992a), and the extract was subjected to preparative thin-layer chromatography (TLC) on C_{18} reversed-phase plates (20 × 20 cm, layer thickness = 1000 μm; Whatman Chemical Separation, Inc.). As described previously (Khachik et al., 1992a), band one (R_f = 0.65, 4-cm width) was separated and further subjected to semipreparative HPLC (eluent E) on a nitrile-bonded column for the isolation of several dietary carotenoids and their oxidative metabolites including those of lycopene. The isolated lycopene metabolites were identified by comparison of their HPLC-UV−vis/MS profiles on a reversed-phase (eluent A) and a nitrile-bonded column (eluent E) with those of reference compounds prepared by partial synthesis.

Partial Synthesis of Lycopene Epoxides. To a solution of lycopene (96% pure, 1.0 g, 0.0019 mol) in 250 mL of tetrahydrofuran [THF, with no butylated hydroxytoluene (BHT)] containing solid sodium bicarbonate (0.50 g, 0.006 mol) was added MCPBA (86% pure, 0.5 g∼0.43 g 100% pure, 0.0025 mol) in THF (40 mL) in 45 min under an atmosphere of nitrogen at room temperature. The progress of the reaction was followed by HPLC (eluent A) at various intervals. Four hours after the addition of MCPBA was completed, the product was partitioned between a 5% solution of $NaHCO_3$ (250 mL) and dichloromethane (300 mL, containing 1% DIPEA). The organic layer was removed, dried over sodium sulfate, and evaporated to dryness to give 2.50 g of a red crude product, which was shown by HPLC-UV−vis/MS (eluent A) to consist of a number of lycopene epoxides, which in the order of elution were tentatively identified as lycopene 5,6;5′,6′-diepoxide (2%, λ_{max} = 440 nm, MS = 568), lycopene 1,2;1′,2′-diepoxide (3%, λ_{max} = 472 nm, MS = 568), lycopene 1,2;5,6-diepoxide (8%, λ_{max} = 456 nm, MS = 568), lycopene 1,2;5′,6′-diepoxide (6%, λ_{max} = 456 nm, MS = 568), lycopene 1,2-epoxide (18%, λ_{max} = 472 nm, MS = 552), lycopene 5,6-epoxide (25%, λ_{max} = 456 nm, MS = 552), and unreacted lycopene (38%, λ_{max} = 472 nm, MS = 536). This mixture was subjected to flash column chromatography as follows.

Purification of Lycopene Epoxides by Flash Column Chromatography. Preliminary purification of lycopene epoxides was accomplished by flash column chromatography (Still et al., 1978). Because flash column chromatography resulted in partial separation of various carotenoids, certain fractions were combined and then subjected to semipreparative HPLC for final purification. A flash column (40-cm length × 4-cm i.d.) was packed with 90 g of n-silica gel (60−200 mesh) using petroleum ether (PE; bp 30−60 °C). This corresponded to the height of 32 cm for the packing. The crude reaction product (2.50 g) was loaded onto the column using ∼15 mL of dichloromethane/0.5% DIPEA, and the column was sequentially eluted with the following eluents. Seventeen fractions (each 125 mL) at the rate of 1 in./min were collected and examined by HPLC (eluent B). Fractions 1−4 were eluted with PE, fractions 5−12 with PE/acetone 90:10, and fractions 13−17 with PE/acetone 80:20. Although fractions 1 and 4−7 did not contain carotenoids and were discarded, the following fractions were combined and identified as follows.

Fractions 2−3. These were shown by HPLC-UV−vis/MS to be unreacted lycopene.

Fractions 6−8. The combined fractions were shown by HPLC-UV−vis/MS to consist of two major and one minor component which were further separated by semipreparative HPLC (eluent C). Each of the isolated fractions was purified for a second time by semipreparative HPLC (eluent C) and were identified in the order of elution as follows.

*2,6-Cyclolycopene-1,5-epoxide B (**IX**):* minor component, HPLC retention time (eluent C) = 18.6 min; UV−vis (hexane) λ_{max} = 281.5, 347, 431, 456.5 (main maximum), 488 nm, (CH_2Cl_2) λ_{max} = 285.5, 352.5, 441, 466.5 (main maximum), 499.5 nm; mass spectrum (ECNI, methane) molecular anion at *m*/*z* 552 (100%); ^{1}H NMR δ 2.00 (H−C-2, m), 1.33 and 1.67 (H_2C-3, m), 1.39 and 1.60 (H_2C-4, m), 2.26 (H−C-6, d, $J_{6/7}$ = 8.1 Hz), 6.28 (H−C-7, dd, $J_{7/6}$ = 8.1 Hz, $J_{7/8}$ = 15.8 Hz), 6.34 (H−C-8, d, $J_{8/7}$ = 15.8 Hz), 6.34 (H−C-10, d, $J_{10/11}$ = 11.3 Hz), 6.75 (H−C-11, dd, $J_{11/10}$ = 11.3 Hz, $J_{11/12}$ = 15.1 Hz), 6.51 (H−C-12, d, $J_{12/11}$ = 15.1 Hz), ∼6.33 (H−C-14, m), ∼6.68 (H−C-15, m), 1.201 (Me-16, s), 1.357 (Me-17, s), 1.299 (Me-18, s), 1.916 (Me-19, s), 1.855 (Me-20, s), 5.22 (H−C-2′, m), 2.18 (H_2−C-3′, m), 2.15 (H_2−C-4′, m), 6.15 (H−C-6′, d, $J_{6'/7'}$ = 11.1 Hz), 6.66 (H−C-7′, dd, $J_{7'/6'}$ = 11.1 Hz, $J_{7'/8'}$ = 15.1 Hz), 6.43 (H−C-8′, d, $J_{8'/7'}$ = 15.1 Hz), 6.35 (H−C-10′, d, $J_{10'/11'}$ = 11.5 Hz), 6.76 (H−C-11′, dd, $J_{11'/10'}$ = 11.5 Hz, $J_{11'/12'}$ = 14.9 Hz), 6.48 (H−C-12′, d, $J_{12'/11'}$ = 14.9 Hz), ∼6.33 (H−C-14′, m), ∼6.68 (H−C-15′, m), 1.650 (Me-16′, s), 1.559 (Me-17′, s), 1.740 (Me-18′, s), 1.916 (Me-19′, s), and 1.865 (Me-20′, s); ^{13}C NMR C-1 and C-1′ (not assigned) δ 54.5 (C-2), 25.2 (C-3), 35.0 (C-4), C-5 and C-5′ (not assigned), 57.9 (C-6), 129.0 (C-7), 136.6 (C-8), C-9 and C-9′ (not assigned), 131.0 (C-10), 125.2 (C-11, C-11′), 137.8 (C-12), C-13 and C-13′ (not assigned), 132.8 and 133.00 (C-14 and C-14′, assignments may be interchanged), 130.30 (C-15 and C-15′), 27.8 (C-16), 28.9 (C-17), 17.9 (C-18), 12.2 (C-19, C-19′, C-20, C-20′), 123.9 (C-2′), 26.3 (C-3′), 39.9 (C-4′), 126.3 (C-6′), 125.0 (C-7′), 135.6 (C-8′), 132.2 (C-10′), 137.5 (C-12′), 25.2 (C-16′), 16.9 (C-17′), and 16.2 (C-18′).

*Lycopene 1,2-epoxide (**II**):* major component, HPLC retention time (eluent C) = 20.1 min, UV−vis (PE) λ_{max} = 444, 470 (main maximum), 502 nm [lit. λ_{max} = 443, 469, 500 nm (Ben-Aziz et al., 1973)]; mass spectrum (ECNI, methane) molecular anion at *m*/*z* 552 (100%); ^{1}H NMR δ 2.56 (H−C-2, dd, $J_{2/3}$ = 6.7 Hz, $J_{2/3b}$ = 5.6 Hz), ∼1.57 (H−C-3a and H−C-3b, m), 2.11 (H−C-4a, m), 2.20 (H−C-4b, m), 6.11 (H−C-6, d, $J_{6/7}$ = 11.1 Hz), 6.63 (H−C-7, dd, $J_{7/6}$ = 11.1 Hz, $J_{7/8}$ = 15.2 Hz), 6.42 (H−C-8, d, $J_{8/7}$ = 15.2 Hz), 6.34 (H−C-10, d, $J_{10/11}$ = 11.6 Hz), 6.76 (H−C-11, dd, $J_{11/10}$ = 11.6 Hz, $J_{11/12}$ = 14.9 Hz), 6.48 (H−C-12, d, $J_{12/11}$ = 14.9 Hz), 6.34 (H−C-14, m), 6.69 (H−C-15, m), 1.10 (Me-16, s), 1.14 (Me-17, s), 1.69 (Me-18, d, $J_{18/6}$ = 0.6 Hz), 1.92 (Me-19, s), 1.87 (Me-20, s), 5.23 (H−C-2′, tt, $J_{2'/3'}$ = 6.8 Hz, $J_{2'/4'}$ = 1.4 Hz), ∼2.11 (H_2C-3′, m), ∼2.18 (H_2C-4′, m), 6.15 (H−C-6′, d, $J_{6'/7'}$ = 11.1 Hz), 6.66 (H−C-7′, dd, $J_{7'/6'}$ = 11.1 Hz, $J_{7'/8'}$ = 15.1 Hz), 6.43 (H−C-8′, d, $J_{8'/7'}$ = 15.1 Hz), 6.36 (H−C-10′, d, $J_{10'/11'}$ = 11.6 Hz), 6.76 (H−C-11′, dd, $J_{11'/10'}$ = 11.6 Hz, $J_{11'/12'}$ = 14.9 Hz), 6.49 (H−C-12′, d, $J_{12'/11'}$ = 14.9 Hz), 6.34 (H−C-14′, m), 6.69 (H−C-15′, m), 1.66 (Me-16′, d, $J_{16'/2'}$ = 1.0 Hz), 1.57 (Me-17′, d, $J_{17'/2'}$ = 0.8 Hz), 1.74 (Me-18′, d, $J_{18'/6'}$ = 0.8 Hz), 1.92 (Me-19′, s), and 1.87 (Me-20′, s); ^{13}C NMR δ 57.47 (C-1), 63.34 (C-2), 27.95 (C-3), 37.27 (C-4), 138.02 (C-5), 126.99 (C-6), 125.01 (C-7), 136.45 (C-8), 136.21 (C-9), 132.35 (C-10), 125.55 (C-11), 137.96 (C-12), 136.72 and 136.85 (C-13 and C-13′, assignments may be interchanged), 133.33 and 133.47 (C-14 and C-14′, assignments may be interchanged), 130.64 and 130.76 (C-15 and C-15′, assignments may be interchanged), 24.91 (C-16), 18.89 (C-17), 16.85 (C-18), 12.95 (C-19), 12.84 (C-20), 131.57 (C-1′), 124.49 (C-2′), 27.10 (C-3′), 40.61 (C-4′), 138.97 (C-5′), 126.76 (C-6′), 125.30 (C-7′), 136.15 (C-8′), 136.40 (C-9′), 132.58 (C-10′), 125.68 (C-11′), 133.15 (C-12′), 25.81 (C-16′), 17.72 (C-17′), 16.89 (C-18′), 12.95 (C-19′), and 12.84 (C-20′).

*2,6-Cyclolycopene-1,5-epoxide A (**VIII**):* major component, HPLC retention time (eluent C) = 23.6 min, UV−vis (hexane) λ_{max} = 281.5, 346, 430.5, 456.5 (main maximum), 488 nm, (CH_2Cl_2) λ_{max} = 285.5, 352, 441, 466.5 (main maximum), 499.5 nm; mass spectrum (ECNI, methane) molecular anion at *m*/*z* 552

(100%); ^{1}H NMR δ 1.88 (H−C-2, m), 1.70 and 1.78 (H_2C-3, m), 1.50 and 1.56 (H_2C-4, m), 2.88 (H−C-6, d, $J_{6/7}$ = 8.7 Hz), 5.63 (H−C-7, dd, $J_{7/6}$ = 8.7 Hz, $J_{7/8}$ = 15.5 Hz), 6.41 (H−C-8, d, $J_{8/7}$ = 15.5 Hz), 6.30 (H−C-10, d, $J_{10/11}$ = 11.8 Hz), 6.76 (H−C-11, dd, $J_{11/10}$ = 11.8 Hz, $J_{11/12}$ = 15.2 Hz), 6.52 (H−C-12, d, $J_{12/11}$ = 15.2 Hz), ∼6.34 (H−C-14, m), ∼6.70 (H−C-15, m), 1.238 (Me-16, s), 1.223 (Me-17, s), 1.342 (Me-18, s), 1.868 (Me-19, s), 1.873 (Me-20, s), 5.23 (H−C-2′, m), 2.20 (H_2−C-3′, m), 2.15 (H_2−C-4′, m), 6.15 (H−C-6′, d, $J_{6'/7'}$ = 10.9 Hz), 6.66 (H−C-7′, dd, $J_{7'/6'}$ = 10.9 Hz, $J_{7'/8'}$ = 15.1 Hz), 6.43 (H−C-8′, d, $J_{8'/7'}$ = 15.1 Hz), 6.35 (H−C-10′, d, $J_{10'/11'}$ = 11.6 Hz), 6.77 (H−C-11′, dd, $J_{11'/10'}$ = 11.6 Hz, $J_{11'/12'}$ = 15.1 Hz), 6.48 (H−C-12′, d, $J_{12'/11'}$ = 15.1 Hz), ∼6.34 (H−C-14′, m), ∼6.70 (H−C-15′, m), 1.664 (Me-16′, s), 1.558 (Me-17′, s), 1.739 (Me-18′, s), 1.917 (Me-19′, s), and 1.868 (Me-20′, s); ^{13}C NMR δ 78.86 (C-1), 52.19 (C-2), 22.85 (C-3), 33.44 (C-4), 87.04 (C-5), 57.48 (C-6), 126.32 (C-7), 138.28 (C-8), 135.21 (C-9), 131.94 (C-10), 125.22 (C-11), 138.32 (C-12), 136.45, 136.50 and 136.92 (C-9′, C-13 and C-13′, assignments may be interchanged), 133.24 and 133.52 (C-14 and C-14′, assignments may be interchanged), 130.53 and 130.85 (C-15 and C-15′, assignments may be interchanged), 25.99 (C-16), 29.44 (C-17), 18.88 (C-18), 13.02 (C-19), 12.84 and 12.85 (C-20, C-20′, assignments may be interchanged), 131.57 (C-1′), 124.49 (C-2′), 27.10 (C-3′), 40.61 (C-4′), 139.01 (C-5′), 126.75 (C-6′), 125.34 (C-7′), 136.13 (C-8′), 132.32 (C-10′), 125.73 (C-11′), 137.92 (C-12′), 25.82 (C-16′), 17.73 (C-17′), 16.89 (C-18′), and 12.96 (C-19′).

Fractions 9−12. The combined fractions were shown by HPLC-UV−vis/MS to consist of one major and one minor component, which were further separated by semipreparative HPLC (eluent D). Each of the isolated compounds was purified for a second time by semipreparative HPLC (eluent D) and was identified in the order of elution as follows.

*1,16-Didehydro-2,6-cyclolycopen-5-ol (**XII**):* major component, HPLC retention time (eluent D) = 21.7 min, UV−vis (hexane) λ_{max} = 280.5, 345.5, 429.5, 454.5 (main maximum), 486 nm, (CH_2Cl_2) λ_{max} = 351, 440, 465 (main maximum), 498 nm; mass spectrum (ECNI, methane) molecular anion at *m*/*z* 552 (100%); ^{1}H NMR δ 2.97 (H−C-2, ddd, pseudo-hextet at ∼2.91−3.04 ppm), ∼2.00 (H−C-3a, m), ∼1.48 (H−C-3b, m), ∼1.72 (H−C-4a, m), ∼1.60 (H−C-4b, m), 2.14 (H−C-6, dd, $J_{6/2}$ = 11.0 Hz, $J_{6/7}$ = 8.7 Hz), 5.80 (H−C-7, dd, $J_{7/6}$ = 15.8 Hz, $J_{7/8}$ = 8.7 Hz), 6.31 (H−C-8, d, $J_{8/7}$ = 15.8 Hz), 6.27 (H−C-10, d, $J_{10/11}$ = 11.4 Hz), 6.72 (H−C-11, dd, $J_{11/12}$ = 14.9 Hz, $J_{11/10}$ = 11.4 Hz), 6.47 (H−C-12, H−C-12′, d, $J_{12/11}$ = $J_{12'/11'}$ = 15.1 Hz), 6.32 (H−C-14, H−C-14′, m), 6.68 (H−C-15, H−C-15′, m), 4.90 (H−C-16a, m), 4.83 (H−C-16b, m), 1.66 (Me-17, n/m), 1.13 (Me-18, s), 1.85 (Me-19, b/s), 1.84 (Me-20, b/s), 5.23 (H−C-2′, m), 2.16 (H−C-3′, H−C-4′, m), 6.15 (H−C-6′, d, $J_{6'/7'}$ = 10.9 Hz), 6.66 (H−C-7′, dd, $J_{7'/8'}$ = 15.2 Hz, $J_{7'/6'}$ = 10.9 Hz), 6.43 (H−C-8′, d, $J_{8'/7'}$ = 15.2 Hz), 6.34 (H−C-10′, d, $J_{10'/11'}$ = 11.6 Hz), 6.76 (H−C-11′, dd, $J_{11'/12'}$ = 15.1 Hz, $J_{11'/10'}$ = 11.6 Hz), 1.66 (Me-16′, n/m), 1.56 (Me-17′, n/d, $J_{17'/2'}$ ∼ 0.9 Hz), 1.74 (Me-18′, n/d), 1.92 (Me-19′, b/s), and 1.86 (Me-20′, b/s); ^{13}C NMR δ 146.98 (C-1), 51.37 (C-2), 28.65 (C-3), 40.26 (C-4), 58.42 (C-6), 127.88 (C-7), 138.07 (C-8), 131.72 (C-10), 125.37 (C-11), 138.31 (C-12), 133.28 (C-14, C-14′), 130.59 (C-15), 110.67 (C-16), 20.14 (C-17), 27.11 (C-18), 13.09 (C-19), 12.84 (C-20), 131.64 (C-1′), 124.51 (C-2′), 27.22 (C-3′), 40.60 (C-4′), 138.95 (C-5′, tentative), 126.76 (C-6′), 125.29 (C-7′), 136.65 (C-8′), 136.1 (C-9′), 132.33 (C-10′), 125.65 (C-11′), 137.96 (C-12′), 130.71 (C-15′), 25.80 (C-16′), 17.77 (C-17′), 16.88 (C-18′), 12.96 (C-19′), and 12.84 (C-20′).

*Lycopene 1,2;1′,2′-diepoxide (**VII**):* minor component, HPLC retention time (eluent D) = 25.2 min, UV−vis (hexane) λ_{max} = 282, 293, 345, 445.5, 470 (main maximum), 500 nm, (CH_2Cl_2) λ_{max} = 288, 298, 350.5, 456.5, 481 (main maximum), 512.0.5 nm; mass spectrum (ECNI, methane) molecular anion at *m*/*z* 568 (100%); ^{1}H NMR δ 2.56 (H−C-2, dd, $J_{2/3a}$ = 6.6 Hz, $J_{2/3b}$ = 5.8 Hz), ∼1.57 (H−C-3a and H−C-3b, m), 2.11 (H−C-4a, m), 2.19 (H−C-4b, m), 6.11 (H−C-6, d, $J_{6/7}$ = 10.9 Hz), 6.63 (H−C-7, dd, $J_{7/6}$ = 10.9 Hz, $J_{7/8}$ = 15.1 Hz), 6.42 (H−C-8, d, $J_{8/7}$ = 15.1 Hz), 6.35 (H−C-10, d, $J_{10/11}$ = 11.5 Hz), 6.76 (H−C-11, dd, $J_{11/10}$ = 11.5 Hz, $J_{11/12}$ = 14.8 Hz), 6.49 (H−C-12, d, $J_{12/11}$ = 14.8 Hz), 6.34 (H−C-14, H−C-14′, m), 6.69 (H−C-15, H−C-15′, m), 1.10 (Me-16, Me-16′, s), 1.14 (Me-17, Me-17′, s), 1.69 (Me-18, Me-18′, s, broad), 1.92 (Me-19, Me-19′, s), 1.87 (Me-20, Me-20′, s), 2.56 (H−C-2′, dd, $J_{2'/3'a}$ = 6.6 Hz, $J_{2'/3'b}$ = 5.8 Hz), ∼1.57 (H−C-3′a and H−C-3′b, m), 2.11 (H−C-4′a, m), 2.19 (H−C-4′b, m), 6.11 (H−C-6′, d, $J_{6'/7'}$ = 10.9 Hz), 6.63 (H−C-7′, dd, $J_{7'/6'}$ = 10.9 Hz, $J_{7'/8'}$ = 15.1 Hz), 6.42 (H−C-8′, d, $J_{8'/7'}$ = 15.1 Hz), 6.35 (H−C-10′, d, $J_{10'/11'}$ = 11.5 Hz), 6.76 (H−C-11′, dd, $J_{11'/10'}$ = 11.5 Hz, $J_{11'/12'}$ = 14.8 Hz), and 6.49 (H−C-12′, d, $J_{12'/11'}$ = 14.8 Hz); ^{13}C NMR δ 57.48 (C-1, C-1′), 63.35 (C-2, C-2′), 27.96 (C-3, C-3′), 37.28 (C-4, C-4′), 138.06 (C-5, C-5′), 127.00 (C-6, C-6′), 125.02 (C-7, C-7′), 136.46 (C-8, C-8′), 136.25 (C-9, C-9′), 132.58 (C-10, C-10′), 125.60 (C-11, C-11′), 138.14 (C-12, C-12′), 136.80 (C-13, C-13′), 133.45 (C-14 and C-14′), 130.73 (C-15 and C-15′), 24.92 (C-16, C-16′), 18.90 (C-17, C-17′), 16.86 (C-18, C-18′), 12.96 (C-19, C-19′), and 12.85 (C-20, C-20′).

Fractions 13−17. The combined fractions were shown by HPLC-UV−vis/MS to consist of one major and one minor component, which were further separated by semipreparative HPLC (eluent E). Each of the isolated fractions was further purified by semipreparative HPLC for a second time and identified in the order of elution as follows.

*2,6-Cyclolycopene-1,5-diol A (**X**):* major component, HPLC retention time (eluent E) = 17.0 min, UV−vis (hexane) λ_{max} = 281, 346.5, 431.5, 456.5 (main maximum), 488.5 nm, (CH_2Cl_2) λ_{max} = 285, 352, 441, 468.5 (main maximum), 499 nm; mass spectrum (ECNI, methane) molecular anion at *m*/*z* 570 (100%); ^{1}H NMR δ 2.32 (H−C-2, ddd, $J_{2/3a}$∼ $J_{2/3b}$ = 9.9 Hz, $J_{2/6}$ = 6.9 Hz), 1.97 (H−C-3a, m), 1.52 (H−C-3b, m), 1.81 (H−C-4a, ddd, J_{gem}∼ 17, $J_{4a/3a}$ = 8.4 Hz, $J_{4a/3b}$ = 3.8 Hz), 1.68 (H−C-4b, ddd, J_{gem}∼ 17 Hz, $J_{4b/3a}$ = 5.0 Hz, $J_{4b/3b}$ = 3.8 Hz), 2.25 (H−C-6, m, $J_{6/7}$ = 9.0 Hz, $J_{6/2}$ = 6.9 Hz), 5.74 (H−C-7, dd, $J_{7/6}$ = 9.0 Hz, $J_{7/8}$ = 15.8 Hz), 6.25 (H−C-8, d, $J_{8/7}$ = 15.8 Hz), 6.16 (H−C-10, d, $J_{10/11}$ = 11.3 Hz), 6.60 (H−C-11, dd, $J_{11/10}$ = 11.3 Hz, $J_{11/12}$ = 14.9 Hz), 6.36 (H−C-12, H−C-12′, d, $J_{12/11}$ = $J_{12'/11'}$ = 14.9 Hz), ∼6.26 (H−C-14, H−C-14′, m), ∼6.63 (H−C-15, H−C-15′, m), 1.167 and 1.188 (Me-16, Me-17, s, signal assignments may be interchanged), 1.238 (Me-18, s), 1.939 (Me-19, s), 1.97 (Me-19′, Me-20, Me-20′, s), 5.11 (H−C-2′, m), ∼2.11 (H_2−C-3′, H_2−C-4′, m), 5.96 (H−C-6′, d, $J_{6'/7'}$ = 11.0 Hz), 6.50 (H−C-7′, dd, $J_{7'/6'}$ = 11.0 Hz, $J_{7'/8'}$ = 15.1 Hz), 6.25 (H−C-8′, d, $J_{8'/7'}$ = 15.1 Hz), 6.19 (H−C-10′, d, $J_{10'/11'}$ = 11.1 Hz), 6.64 (H−C-11′, dd, $J_{11'/10'}$ = 11.1 Hz, $J_{11'/12'}$ = 14.9 Hz), 6.36 (H−C-12′, d, $J_{12'/11'}$ = 14.9 Hz), 1.691 (Me-16′, s), 1.618 (Me-17′, s), and 1.822 (Me-18′, s); ^{13}C NMR δ 73.13 (C-1), 54.30 (C-2), 25.11 (C-3), 39.76 (C-4), 82.17 (C-5), 55.61 (C-6), 129.39 (C-7), 138.17 (C-8), 134.86 (C-9), 131.51 (C-10), 124.63 (C-11), 137.99 (C-12), 136.23 (C-13), 132.86 (C-14), 130.29 (C-15), 28.51 and 27.35 (C-16, C-17, assignments may be interchanged), 26.68 (C-18), 13.08 (C-19), 12.79 (C-20, C-20′), 131.75 (C-1′), 123.94 (C-2′), 26.68 (C-3′), 40.23 (C-4′), 139.54 (C-5′), 125.71 (C-6′), 124.84 (C-7′), 135.38 (C-8′), 136.31 (C-9′), 131.59 (C-10′), 125.24 (C-11′), 137.30 (C-12′), 136.69 (C-13′), 132.54 (C-14′), 129.93 (C-15′), 25.69 (C-16′), 17.69 (C-17′), 16.95 (C-18′), and 12.90 (C-19′).

*2,6-Cyclolycopene-1,5-diol B (**XI**):* minor component, HPLC retention time (eluent E) = 23.2 min, UV−vis (hexane) λ_{max} = 280.5, 346.5, 430.5, 455.5 (main maximum), 488 nm, (CH_2Cl_2) λ_{max} = 284, 351, 440.5, 466 (main maximum), 498.5 nm; mass spectrum (ECNI, methane) molecular anion at *m*/*z* 570 (100%); ^{1}H NMR δ ∼1.96 (H−C-2, m, overlapped), 1.78 (H−C-3a, m, overlapped), 1.80 (H−C-3b, m, overlapped), 1.68 (H−C-4a, m, overlapped), 1.71 (H−C-4b, m, overlapped), 2.52 (H−C-6, dd, $J_{6/7}$ = 9.9 Hz, $J_{6/2}$ = 5.2 Hz), 5.48 (H−C-7, dd, $J_{7/6}$ = 9.9 Hz, $J_{7/8}$ = 15.4 Hz), 6.15 (H−C-8, d, $J_{8/7}$ = 15.4 Hz), 6.13 (H−C-10, d, $J_{10/11}$ = 11.5 Hz), 6.59 (H−C-11, dd, $J_{11/10}$ = 11.5 Hz, $J_{11/12}$ = 14.9 Hz), 6.35 (H−C-12, H−C-12′, d, $J_{12/11}$ = 14.9 Hz, $J_{12'/11'}$ = 14.8 Hz), ∼6.26 (H−C-14, H−C-14′, m), ∼6.63 (H−C-15, H−C-15′, m), 1.242 and 1.205 (Me-16, Me-17, s, signal assignments may be interchanged), 1.163 (Me-18, s), 1.902 (Me-19, s), 1.967 (Me-20, Me-20′, s), 5.11 (H−C-2′, m), ∼2.11 (H_2−C-3′, H_2−C-4′, m), 5.95 (H−C-6′, d, $J_{6'/7'}$ = 11.1 Hz), 6.49 (H−C-7′, dd, $J_{7'/6'}$ = 11.1 Hz, $J_{7'/8'}$ = 15.1 Hz), 6.25 (H−C-8′, d, $J_{8'/7'}$ = 15.1 Hz), 6.18 (H−C-10′, d, $J_{10'/11'}$ = 11.4 Hz), 6.64 (H−C-11′, dd, $J_{11'/10'}$ = 11.4 Hz, $J_{11'/12'}$ = 14.8 Hz), 1.684 (Me-16′, s), 1.611 (Me-17′, s), 1.817 (Me-18′, s), and 1.960 (C-19′); ^{13}C NMR δ 72.46 (C-1), 55.19 (C-2), 24.14 (C-3), 39.62 (C-4), 81.35

(C-5), 56.32 (C-6), 131.74 (C-7), 135.23 (C-8), C-9 and C-9′ (not assigned), 130.95 (C-10), ~124.45 (C-11), ~137.49 (C-12, C-12′), C-13 and C-13′ (not assigned), ~132.44 (C-14, C-14′), ~129.91 (C-15, C-15′), 29.22 and 28.11 (C-16, C-17, assignments may be interchanged), 23.95 (C-18), 13.04 (C-19), 12.89 (C-20), C-1′ (not assigned), 123.97 (C-2′), 26.71 (C-3′), 40.03 (C-4′), C-5′ (not assigned), 125.49 (C-6′), 124.51 (C-7′), 135.36 (C-8′), 131.31 (C-10′), 124.82 (C-11′), ~137.30 (C-12′), 25.64 (C-16′), 17.53 (C-17′), 16.76 (C-18′), 12.89 (C-19′), and 12.78 (C-20′).

Quantitative Analysis of Lycopene Oxidation Products after Column Chromatography on n-Silica Gel. A crude mixture of lycopene epoxides, prepared from the reaction of lycopene and MCPBA, was loaded on a flash column packed with n-silica gel as described earlier. All of the pigments were eluted as one fraction using PE/acetone = 50:50. This was shown by HPLC-UV−vis/MS (eluent B) to consist of **I** (38%), **II** (15%), **VII** (2%), **VIII** (12%), **IX** (2%), **X** (12%), **XI** (4%), **XII** (10%), and several unidentified products (5%).

In Situ Hydrolysis of a Crude Mixture of Lycopene Epoxides. Lycopene epoxides were prepared from the oxidation of lycopene (0.5 g) with MCPBA in THF (300 mL), the same as above but the addition of sodium bicarbonate was eliminated. The crude mixture of unreacted lycopene and lycopene epoxides was hydrolyzed under two different sets of conditions as described below.

1. Hydrolysis with 1% H_2SO_4 in Acetone. The above crude mixture in THF (300 mL) was treated with 5 mL of 1% H_2SO_4 in spectrophotometric grade acetone under an atmosphere of nitrogen for 15 min. The product was treated with 2 mL of DIPEA and partitioned between a solution of 10% sodium bicarbonate (200 mL) and dichloromethane (200 mL). The organic layer was removed, dried over Na_2SO_4, and evaporated to dryness. The major products of this reaction were shown by HPLC-UV−vis/MS (eluent B) to consist of recovered **I** (36%), a mixture of several unidentified byproducts (16%), **VIII** (1%), **IX** (0.2%), **X** (14%), **XI** (3.8%), **XII** (20%), and an unknown (**XIII**, 9%). This unknown was separated by flash column chromatography using identical conditions described earlier. The partially purified compound, which was enriched in fractions 6−8 of flash, was purified twice by semipreparative HPLC (eluent C) and identified as the following.

*Lycopene 1,6;2,5-diepoxide (**XIII**):* HPLC retention time (eluent C) = 25.8 min; UV−vis (hexane) λ_{max} = 280.5, 346, 429.5, 455, 487 nm, (CH_2Cl_2) λ_{max} = 284.5, 351, 439.5, 465, 497.5 nm; mass spectrum (ECNI, methane) ion at *m/z* 568 (100%); ^{1}H NMR δ 3.67 (H−C-2, d, $J_{2/3a}$ = 7.1 Hz, $J_{2/3b}$ ~ 0 Hz), 1.71 (H−C-3a, m), 2.02 (H−C-3b, m), 1.22 (H−C-4a, m), 2.09 (H−C-4b, m), 4.37 (H−C-6, d, $J_{6/7}$ = 6.3 Hz), 5.64 (H−C-7, dd, $J_{7/6}$ = 6.3 Hz, $J_{7/8}$ = 15.7 Hz), 6.61 (H−C-8, d, $J_{8/7}$ = 15.7 Hz), 6.27 (H−C-10, d, $J_{10/11}$ = 11.2 Hz), 6.68 (H−C-11, dd, $J_{11/10}$ = 11.2 Hz, $J_{11/12}$ = 15.0 Hz), 6.43 (H−C-12, d, $J_{12/11}$ = 15.0 Hz), 6.29 (H−C-14, AA′BB′ spin system with H−C-14′, H−C-15, H−C-15′, overlapped with H−C-10, H−C-10′), 6.66 (H−C-15, AA′BB′ spin system with H−C-14, H−C-14′, H−C-15′, covered with H−C-11 and H−C-7′), 1.04 (Me-16, s), 1.46 (Me-17, s), 1.25 (Me-18, s), 1.80 (Me-19, s), 1.83 (Me-20, s), 5.22 (H−C-2′, m), ~2.18 (H−C-3′, m), ~2.15 (H−C-4′, m), 6.15 (H−C-6′, d, $J_{6'/7'}$ = 11.6 Hz), 6.66 (H−C-7′, dd, $J_{7'/6'}$ = 11.6 Hz, $J_{7'/8'}$ = 15.1 Hz), 6.42 (H−C-8′, d, $J_{8'/7'}$ = 15.1 Hz), 6.34 (H−C-10′, d, $J_{10'/11'}$ = 11.6 Hz), 6.76 (H−C-11′, dd, $J_{11'/10'}$ = 11.6 Hz, $J_{11'/12'}$ = 15.0 Hz), 6.46 (H−C-12′, d, $J_{12'/11'}$ = 15.0 Hz), 6.32 (H−C-14′, AA′BB′ spin system with H−C-14, H−C-15, H−C-15′, overlapped with H−C-10, H−C-10′), 6.67 (H−C-15′, AA′BB′ spin system with H−C-14, H−C-14′, H−C-15, covered with H−C-11, H−C-7′), 1.66 (Me-16′, s), 1.56 (Me-17′, s), 1.74 (Me-18′, s), 1.92 (Me-19′, s), and 1.86 (Me-20′, s); ^{13}C NMR δ 74.84 (C-1), 81.29 (C-2), 25.94 (C-3), 29.47 (C-4), 81.63 (C-5), 79.23 (C-6), 125.97 (C-7), 137.10 (C-8), 134.68 (C-9), 132.72 (C-10), 124.87 (C-11), 138.36 (C-12), 136.17 (C-13), 133.29 (C-14), 130.60 (C-15), 25.40 (C-16), 22.24 (C-17), 21.85 (C-18), 12.59 (C-19), 12.58 (C-20, C-20′), 131.40 (C-1′), 124.20 (C-2′), 26.89 (C-3′), 40.31 (C-4′), 138.78 (C-5′, uncertain), 126.50 (C-6′), 125.02 (C-7′), 135.81 (C-8′), 136.18 (C-9′), 132.02 (C-10′), 125.41 (C-11′), 137.64 (C-12′), 136.73 (C-13′), 132.97 (C-14′), 130.24 (C-15′), 25.57 (C-16′), 17.42 (C-17′), 16.66 (C-18′), and 12.66 (C-19′).

2. Hydrolysis with 0.1% H_2SO_4 in Water. The above crude mixture in THF (300 mL) was treated with 30 mL of 0.1% H_2SO_4 in water under an atmosphere of nitrogen for 24 h. The product was treated with 2 mL of DIPEA and partitioned between a solution of 10% sodium bicarbonate (200 mL) and dichloromethane (200 mL). The organic layer was removed and worked-up as above. The products of this reaction were shown by HPLC-UV−vis/MS (eluent B) in the order of elution to consist of unreacted **I** (38%), **IX** (0.5%), **II** (2%), **VIII** (2%), **XIII** (5%), **XII** (7%), a mixture of several unidentified byproducts (8.5%), **X** (33%), and **XI** (4%). The mixture was subjected to flash column chromatography under the same conditions described earlier to give a pure mixture of **X** (0.119 g) and **XI** (0.022 g).

Hydrolysis of Purified 2,6-Cyclolycopene-1,5-epoxides A (VIII) and B (IX). A sample of **VIII** (~0.2 mg) purified by preparative HPLC was dissolved in THF (0.5 mL) and was treated with 20 μL of 0.1% sulfuric acid in water at room temperature for 24 h. The product was treated with 50 μL of DIPEA and worked-up as above. HPLC-UV−vis/MS (eluent B) of the product showed the complete conversion of compound **VIII** to **X**. In a similar experiment **IX** was converted to **XI**.

Rearrangement of II on n-Silica Gel. A sample of *all-E*-lycopene 1,2-epoxide (**II**), purified by HPLC, was loaded on a flash column packed with n-silica gel as described earlier and was eluted with PE/acetone = 80:20. All of the pigments were collected as one fraction. HPLC-UV−vis/MS (eluent B) of this fraction showed the presence of unreacted **II** (78%, *all-E* + *Z*), **VIII** (11%), **IX** (2%), and a mixture of unidentified products (9%).

Rearrangement of II in 1% H_2SO_4 in Acetone. A sample of *all-E*-lycopene 1,2-epoxide (0.156 mg) in dichloromethane (3 mL) was treated with 10 μL of 1% H_2SO_4 in spectrophotometric grade acetone for 3 min. The product was treated with DIPEA and worked up as described above. The HPLC-UV−vis/MS (eluent B) of the product showed the presence of unreacted **II** (20%), **XII** (51%), and a mixture of unidentified products (29%).

RESULTS AND DISCUSSION

Partial Synthesis of Lycopene Epoxides. The reaction of lycopene with MCPBA (86% pure) did not proceed at 0 °C, but at room temperature lycopene slowly underwent epoxidation to form two major products. These were tentatively identified from their HPLC-UV−vis/MS as lycopene 1,2-epoxide (**II**) and lycopene 5,6-epoxide (**III**). The course of the reaction was followed by HPLC-UV−vis/MS on a reversed-phase (eluent A) and a nitrile-bonded (eluent B) column as shown in parts A and B of Figure 1, respectively. The HPLC peak identification is shown in Figure 2. After 4 h, ~62% of lycopene was shown to have converted to its mono- and diepoxides. When the reaction was allowed to proceed beyond 4 h, the yield of the lycopene diepoxides increased at the expense of the lycopene monoepoxides. The HPLC peak identification of the products was initially based on the UV−vis/MS profiles of the individual components obtained by a photodiode array detector coupled with a particle beam mass spectrometer and was later confirmed by NMR. Exceptions to this were compounds **III**−**VI**, which could not be isolated for structural elucidation by NMR and were therefore tentatively identified by HPLC-UV−vis/MS. Lycopene 5,6-epoxide (**III**, λ_{max} = 456 nm, MS = 552, $C_{40}H_{56}O$) exhibits a 16 nm hypsochromic shift in its UV−vis spectrum when compared to lycopene (**I**, λ_{max} = 472 nm, MS = 536, $C_{40}H_{56}$), indicating the presence of only 10 conjugated double bonds in this compound.

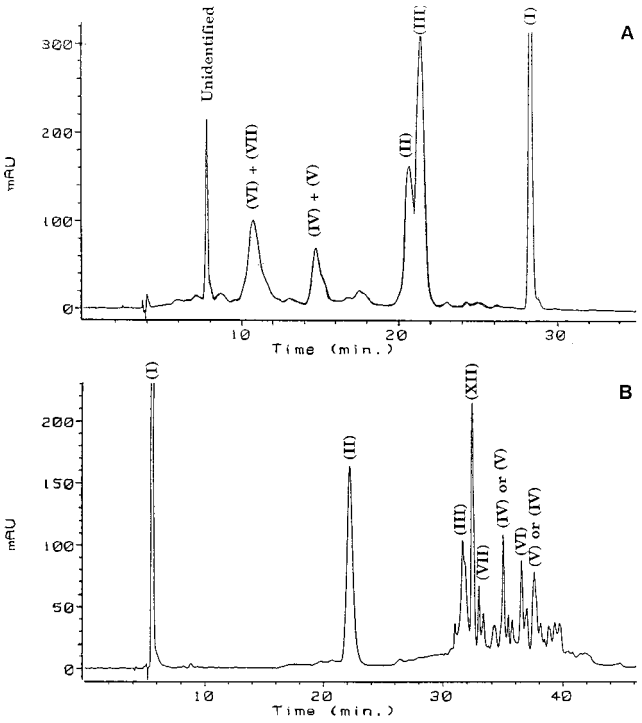

Figure 1. HPLC profiles of the crude products from the reaction of lycopene with MCPBA after 4 h at room temperature: (A) separation on a C_{18} reversed-phase column with eluent A; (B) separation on a silica-based nitrile-bonded column with eluent B. For HPLC peak identification, see Figure 2. HPLC conditions are described in the text.

Meanwhile, the absorption maximum of lycopene 1,2-epoxide (**II**, $\lambda_{max} = 472$ nm, MS = 552, $C_{40}H_{56}O$) remains the same as lycopene because the terminal location of the epoxide at the 1,2-position does not alter the conjugation of the polyene chain. Several of the diepoxides of lycopene that were formed as minor products were similarly identified. Lycopene 5,6;5′,6′-diepoxide (**VI**, $\lambda_{max} = 440$ nm, MS = 568, $C_{40}H_{56}O_2$) shows the presence of only nine conjugated double bonds, pointing to the epoxidation of lycopene at the 5,6- and 5′,6′-positions. On the other hand, in lycopene 1,2;1′,2′-diepoxide (**VII**, $\lambda_{max} = 472$ nm, MS = 568, $C_{40}H_{56}O_2$) the conjugated polyene system remains intact. Unfortunately, in the case of the proposed lycopene 1,2;5,6-diepoxide (**IV**, $\lambda_{max} = 456$ nm, MS = 568, $C_{40}H_{56}O_2$) and lycopene 1,2;5′,6′-diepoxide (**V**, $\lambda_{max} = 456$ nm, MS = 568, $C_{40}H_{56}O_2$), the HPLC/MS data are not sufficient to distinguish between these compounds.

The HPLC profiles shown in Figure 1 were at first confusing because the reversed-phase profile (A) of the crude product showed that the major products of the reaction of lycopene with MCPBA were lycopene 5,6-epoxide (**III**, 25%, tentative identification) and lycopene 1,2-epoxide (**II**, 18%), whereas nitrile-bonded phase chromatography (B) revealed the presence of many products, among which only **II** was found to be the major product. This problem was later clarified when we demonstrated that **III** is not stable on normal phase silica gel and silica gel-based nitrile-bonded adsorbents and undergoes rearrangement to form a number of products. We have also shown that lycopene 1,2-epoxide is stable on silica gel-based nitrile-bonded adsorbent and only partially undergoes rearrangement on n-silica gel to **VIII** and **IX**. In addition, once lycopene 1,2-epoxide was purified by flash chromatography and preparative

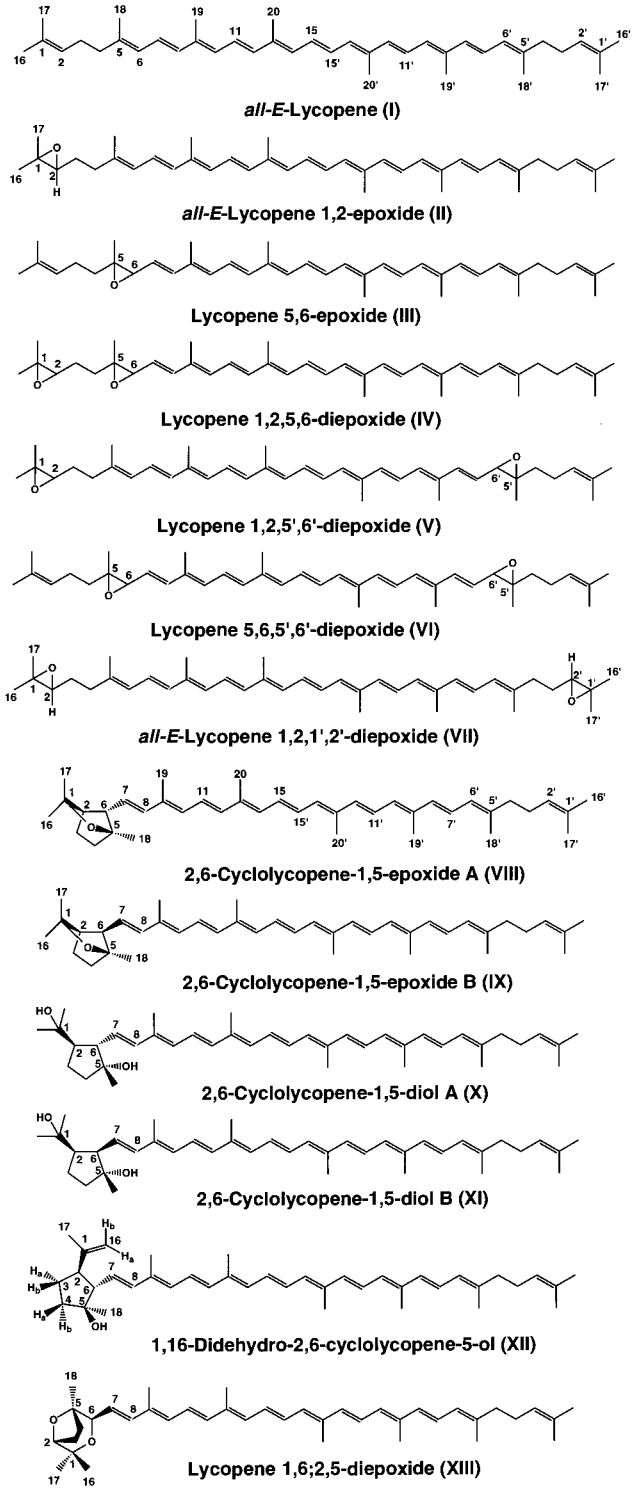

Figure 2. Chemical structure of lycopene and its oxidation products prepared by partial synthesis. For the designated names of carotenoids with novel five-membered ring end-groups, see Nomenclature. Only the relative but not the absolute configurations of the asymmetric centers at C(2), C(5), and C(6) for carotenoids with novel five-membered ring end-groups are known.

HPLC, it was found to be quite stable for structural elucidation. On the other hand, numerous attempts to isolate lycopene 5,6-epoxide by flash column chromatography and preparative HPLC on nitrile-bonded and C_{18} reversed-phase columns were unsuccessful. Nevertheless, for separation and purification of lycopene oxidation and rearrangement products on analytical and

semipreparative scales by HPLC, the nitrile-bonded column was found to be extremely useful.

Rearrangement of Lycopene Epoxides on n-Silica Gel. The crude products of the reaction of lycopene with MCPBA were purified by flash column chromatography followed by repeated semipreparative HPLC. During flash column chromatography, as the eluting carotenoids came into contact with n-silica gel, the column became slightly warm, indicating that perhaps some type of reactions may be taking place. The chemical structures (Figure 2) of the various fractions isolated by flash column and semipreparative HPLC were established by ^{1}H and ^{13}C NMR spectroscopy. However, it must be pointed out that only the relative but not the absolute configurations of the compounds with stereogenic centers at C(2), C(5), and C(6) (Figure 2) are known at present. Among the various lycopene epoxides, lycopene 1,2-epoxide (**II**) and lycopene 1,2;1′,2′-diepoxide (**VII**) were readily isolated and found to be quite stable to allow their characterization. However, none of the mono- and diepoxides of lycopene with one or two epoxides located at the 5,6 and/or 5′,6′-positions were stable enough to allow their isolation and characterization. Instead, a number of lycopene derivatives (compounds **VIII**−**XII**, Figure 2) with novel cyclic end-groups were isolated and characterized. From the chemical structures of the isolated compounds, it appeared that lycopene 5,6-epoxide and perhaps to some degree lycopene 1,2-epoxide may have undergone rearrangement to form a diastereomeric mixture of two bicyclic epoxides **VIII** and **IX** with the inversion of configuration at C(6). Furthermore, the isolation and identification of the diastereomeric diols **X** and **XI** by flash column chromatography of the crude products suggested that these compounds may have been formed from acid-catalyzed ring opening of the epoxides **VIII** and **IX**. Therefore, it seemed quite likely that the acidic n-silica gel during flash chromatography may have been responsible for this rearrangement. Numerous attempts to wash and condition the silica gel with PE/triethylamine or PE/DIPEA did not alter the outcome of flash chromatography. It is interesting to note that these rearrangements were not effected by *m*-chlorobenzoic acid, formed during the epoxidation of lycopene with MCPBA, because in the presence or absence of sodium bicarbonate, the qualitative and quantitative nature of the products of these reactions remained the same.

At first, it was not clear whether compounds **VIII** and **IX** were exclusively formed from the rearrangement of lycopene 5,6-epoxide (**III**) on n-silica gel or lycopene 1,2-epoxide may also be involved in this transformation. This is because **III** could not be isolated for further investigation. However, when a sample of lycopene 1,2-epoxide (**II**), purified by HPLC, was passed through n-silica gel, compounds **VIII** and **IX** were formed in 11 and 2% yields, respectively. The fact that 78% of **II** was recovered in this experiment suggests that epoxides **VIII** and **IX** may, to a lesser extent, be formed from the rearrangement of **II** and perhaps to a greater extent from **III**.

While our research was in progress, Lu et al. (1995) reported on the oxidation of lycopene with hydrogen peroxide (30%) in the presence of sulfuric acid (70%) at 0 °C. The products of this reaction were identified as lycopene 1,2-epoxide and an epoxide that was named 1,5-epoxyiridanyl-lycopene. This epoxide is identical to 2,6-cyclolycopene-1,5-epoxide A (**VIII**) reported here, but its diastereomeric epoxide **IX** was not isolated by Lu et al. (1995). In a more recent paper, Yokota et al. (1997) isolated compound **X** from tomato puree to which they assigned the nomenclature of 1,5-dihydroxyiridanyl-lycopene. These investigators also prepared compound **X** in a low yield (3.3%) from the oxidation of lycopene with acidic hydrogen peroxide, but its diastereomeric diol, **XI**, was not isolated. The structure of this diol is identical to compound **X** reported here.

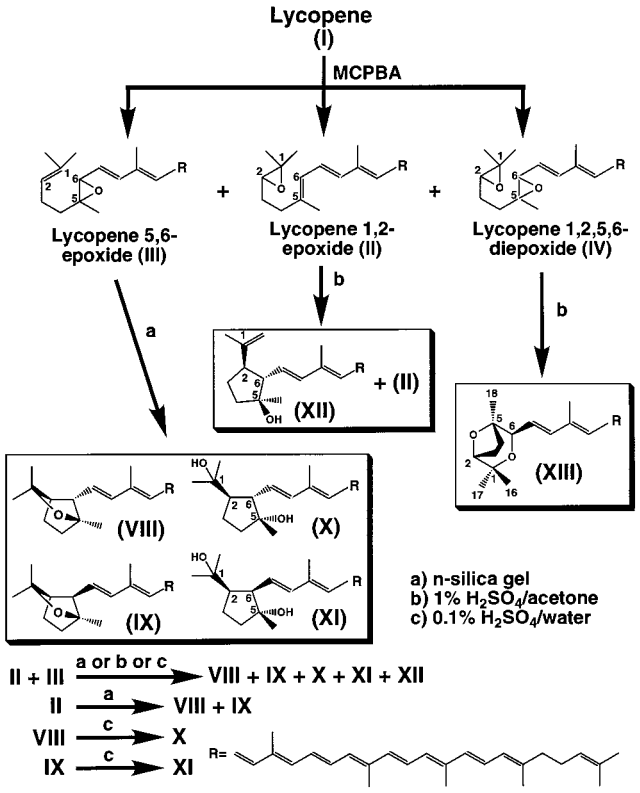

Figure 3. Reaction pathways in the partial synthesis and rearrangement of lycopene oxidation products.

In the following we describe our investigation of the acid-catalyzed rearrangement of lycopene epoxides and present an efficient method for the partial synthesis of the epimeric diols **X** and **XI** from lycopene. The mechanisms leading to the formation of the acid-catalyzed rearrangement products of lycopene epoxides have been discussed in a separate publication (Khachik et al., 1998).

Acid-Catalyzed Rearrangement of Lycopene Epoxides. One of the major objectives of this research was to prepare the diols **X** and **XI** in high yield from lycopene by partial synthesis according to a simple procedure. This was particularly important since, for the first time, we reported on the identification of these compounds from extracts of human serum and milk (Khachik et al., 1997a). Therefore, a series of reactions were carried out to investigate the in situ conversion of the crude lycopene epoxides to these diols. Diols **X** and **XI** were prepared either by passing the crude mixture of lycopene epoxides through n-silica gel or by treatment of this mixture with dilute sulfuric acid as depicted in the reactions in Figure 3. The yields of the various products from these reactions are shown in Table 1.

Although diols **X** and **XI** can be obtained from a crude mixture of lycopene epoxides during purification by flash chromatography on n-silica gel, the highest yield (37%) of these compounds is obtained when the crude mixture

Table 1. Yield (Percent) of the Rearrangement Products of a Crude Mixture of Lycopene Epoxides after Exposure to n-Silica Gel during Flash Chromatography or in Situ Treatment with Dilute Sulfuric Acid[a,b]

		recovered			reaction products (% yield)						
entry	reaction conditions	**I**	**II**	**VII**	**VIII**	**IX**	**X**	**XI**	**XII**	**XIII**	unidentified
1	n-silica gel (flash chromatography)	38	15	2	12	2	12	4	10	0	5
2	1% H_2SO_4 in acetone/15 min	36	0	0	1	0.2	14	3.8	20	9	16
3	0.1% H_2SO_4 in water/24 h	38	2	0	2	0.5	33	4	7	5	8.5

[a] The relative distribution of lycopene and lycopene epoxides in the crude mixture of the starting materials; details of the experimental procedures are described in the text. [b] Yields are based on the HPLC peak area of each compound at the wavelength of its main absorption maximum.

of lycopene epoxides is treated with 0.1% sulfuric acid in water. This mild reaction condition was adapted from that of Eugster (1985), who elegantly hydrolyzed lutein 5,6-epoxide and its 3′-epimer to prepare the respective tetrols of these compounds by partial synthesis. Under this mild hydrolysis condition, the destruction of lycopene epoxides and their rearrangement products can be avoided. The ring opening of pure samples of epoxides **VIII** and **IX** to their respective diols, **X** and **XI**, can be effected almost quantitatively in dilute sulfuric acid in water. This indicates that the rearranged epoxides **VIII** and **IX** may also serve as precursors of their respective diols.

It is interesting to note that in all of the reactions summarized in Table 1 significant amounts of compound **XII** are formed. Although we have shown that **XII** can be obtained from acid-catalyzed rearrangement of purified lycopene 1,2-epoxide, the involvement of lycopene 5,6-epoxide in the formation of this compound remains uncertain. Due to the instability of lycopene 5,6-epoxide and its rearrangement and cyclization reactions, it is quite likely that the lycopene derivatives prepared by Bush and Zechmeister (1958) as well as Ritacco et al. (1984) were not lycopene 5,6-epoxide and its diol but rather 2,6-cyclolycopene-1,5-epoxides (**VIII** and **IX**) and their ring-opening products **X** and **XI**.

The acid-catalyzed hydrolysis of a mixture of lycopene epoxides in dilute sulfuric acid also resulted in the formation of compound **XIII**. On the basis of its chemical structure, this compound is presumably formed from the ring opening and cyclization of lycopene 1,2;5,6-diepoxide.

Structural Elucidation of the Synthetic Compounds by NMR. According to the NMR spectra of the synthetic compounds, in all cases the polyene chain and the primed end-groups were found to be that of original lycopene. In cases where the samples were measured in $CDCl_3$, the proton and carbon-13 chemical shift values were identical to those published by Englert (1995) and Lu et al. (1995). The ^1H resonances were assigned by proton and COSY experiments, and the stereochemical considerations were based on H,H-coupling constant values and T-ROESY results. Carbon-13 assignments were supported by DEPT-135 results as well as by one-bond (HMQC) and long-range (HMBC) proton−carbon correlations. The sample sizes of compounds **IX**, **XI**, **XII**, and **XIII** were not sufficient to perform ^{13}C and DEPT-135 experiments. Therefore, in these cases, most of the ^{13}C shift values were extracted from traces of the inverse HMQC and HMBC experiments with a precision of ±0.30 ppm due to the low digital resolution in 2D matrices. As pointed out under Experimental Procedures, some of the NMR line assignments remain interchangeable due to strong signal overlap, but these overlapping signals do not raise any doubts about the assigned structures. According to the chemical shifts, coupling constant values, and T-ROESY results, all of the synthetic compounds were established to have all-E configuration. No specification of the absolute configurations could be made by NMR for any of the lycopene derivatives.

The T-ROESY spectra of lycopene 1,2-epoxide (**II**) gave information about the spatial position of the proton H(2) in relation to the methyl groups Me(16) and Me-(17). A significant ROE cross-peak between Me(16) and H(2) was detected, suggesting their cis arrangement. The line assignment of the rest of the molecule contained no problem or any significant information that is worth mentioning. The same is valid for the characterization of lycopene 1,2;1′,2′-diepoxide (**VII**). Our NMR results are also in agreement with those of Meier et al. (1986), who prepared (2*R*,2′*R*)-lycopene 1,2;1′,2′-diepoxide by total synthesis.

The bicyclic structure of the end-groups in 2,6-cyclolycopene-1,5-epoxide A (**VIII**) and 2,6-cyclolycopene-1,5-epoxide B (**IX**) could be confirmed as follows. For both compounds the proton nuclei H(2) and H(6) show coupling interactions, visible as COSY cross-peaks, which prove the connection of C(2) with C(6). The significant downfield shifts of the C(1) and C(5) carbon-13 resonances in compound **VIII** in comparison with the corresponding signals in the 1,5-diol (**X**) are due to the ring tension imposed by the 1,5-epoxide bridge. The relative stereochemical arrangement at C(2), C(5), and C(6) could not be established unambiguously. The ^3J[H(2)−H(6)] coupling constant values were found to range below the line widths in both isomers, and whereas Lu et al. (1995) argued that the lack of a NOESY response between H(2) and H(6) indicated their trans position in **VIII**, our T-ROESY experiments show corresponding cross-peaks for both compounds **VIII** and **IX**. Therefore, the comparison of the data (not applicable without some reservation due to the different solvents used) led to the conclusion that the 2,6-cyclolycopene-1,5-epoxide published by Lu et al. (1995) is identical to our isomer A in which H(2)−H(6) are more likely to have a trans arrangement. The ^1H and ^{13}C spectra of the diastereomeric compound **IX** showed some shift deviations in the neighborhood of C(6), mainly affecting H(6), H(7), Me (17), and C(7); these results strongly indicate an inverted configuration at this center. Consequently, a cis arrangement between H(2) and H(6) in compound **IX** is proposed.

The cyclopentane end-groups of 2,6-cyclolycopene-1,5-diol A (**X**) and 2,6-cyclolycopene-1,5-diol B (**XI**) could be proved without doubt on the basis of (a) scalar coupling interactions between H(2) and $H_2C(3)$ as well as between H(2) and H(6) and (b) dipolar ROE interactions between H(6) and both methyl groups Me(16) and Me-(17). The presence of both hydroxyl groups at C(1) and C(5) is verified by the δ values of the quaternary carbon nuclei absorbing at 73.13/82.17 ppm for **X** and at 72.46/

81.35 ppm for **XI** as well as the typical chemical shift values of Me(16) and Me(17). These assignment were based on the effect of the ring tension in the case of C(5), which should shift the resonance to a lower field. The question for the spatial positions between Me(18)/H(2) and H(2)/H(6) could be answered as follows. The ROE signal for diol A is absent between H(2) and H(6) and as a result the position of these protons is fixed in a trans geometry. A scalar coupling as well as a strong ROE interaction between H(6) and Me(18) indicates a cis arrangement for these substituents. The spectra of diol B also showed the latter ROE cross-peak but, in contrast to diol A, it also exhibited a proton−proton coupling interaction between H(2) and H(6). Therefore, in diol B, Me(18)/H(2) and H(2)/H(6) must be arranged in a cis geometry.

The five-membered ring substructure of 1,16-didehydro-2,6-cyclolycopen-5-ol (**XII**) was established using a sequence of scalar interaction in the COSY experiment and characteristic cross-peaks in the T-ROESY spectra. Protons H(16a,b) of the terminal olefin group were identified by two characteristic narrow multiplets at 4.83 and 4.90 ppm, showing long-range couplings to Me-(17) and H(2), and an ROE to H(6). Taking the effect of the ring tension into consideration, further evidence for this five-membered ring end-group was obtained from the chemical shift of H(2) at 2.97 ppm and of C(5) at 81.05 ppm, which are typical for a hydroxyl group attached to a quaternary carbon atom. Overall, the constitution of **XII** is strongly supported by special interaction observed in the T-ROESY spectra and is further confirmed by spectroscopic data of Wolinski et al. (1964) and B. Traber (University of Bern, unpublished results, 1997).

An important clue in the structural elucidation of lycopene 1,6;2,5-diepoxide (**XIII**) was obtained from the molecular mass of 568, indicating a bicyclic end-group instead of a diol. H(6) was found to be one end of the spin system H(6)−H(7)-H(8). Furthermore, the high chemical shift of 4.37 ppm for H(6) indicated a link of C(6) to an ether bridge. Another independent spin system was that of H(2)−H(3a,b)-H(4a,b), in which the downfield shifted H(2) proton at 3.67 ppm was similarly found to be involved in an ether bridge. The main evidence for establishing the connectivities in the ring system of **XIII** was obtained from the $^3J_{C-H}$ coupling of H(2) to C(5) linking C(2) and C(5) through an ether bridge. Therefore, this suggested that C(1) could be connected to C(6) via the second ether bridge; this was further confirmed by an ROE of Me(17) to H(6).

Lycopene Metabolites in Tomato Paste, Tomato Juice, and Human Serum. In 1992 and 1995, we reported that two of the most common oxidation products of lycopene in tomato and tomato products such as paste and juice were lycopene 1,2-epoxide and lycopene 5,6-epoxide (Khachik et al., 1992b; Tonucci et al., 1995). Although lycopene 1,2-epoxide was correctly identified in these food products, the presence of lycopene 5,6-epoxide was established incorrectly. From our extensive study of the epoxidation of lycopene and the acid-catalyzed experiments of the lycopene epoxides, we have now concluded that the misidentified compounds in these foods were in fact 2,6-cyclolycopene-1,5-epoxides A and B (**VIII** and **IX**). This was clearly established by comparison of the HPLC-UV−vis/MS analysis of the extracts from these foods with a mixture of standards prepared by partial synthesis. The HPLC profiles of a mixture of all the purified standards on a C_{18} reversed-phase and a silica-based nitrile-bonded columns are shown in parts A and B of Figure 4, respectively. Certain lycopene oxidation products such as compounds **II**, **XIII**, and **III**, which may not be well separated by reversed-phase chromatography (Figure 4A), are well resolved on a nitrile-bonded column (Figure 4B). This is also the case for compounds **VII** and **X**. It must be pointed out that although the proposed lycopene 5,6-epoxide (**III**) could not be isolated, we have clearly established that this compound elutes immediately after lycopene 1,2-epoxide on a C_{18} reversed-phase column. Furthermore, the HPLC retention time of **III** is considerably different from those of the rearranged epoxides, **VIII** and **IX**. Therefore, after careful examination of the extracts from tomato paste and juice employing a combination of these two HPLC methods, compounds **II** and **VIII**−**XI** were all shown to be present in these foods.

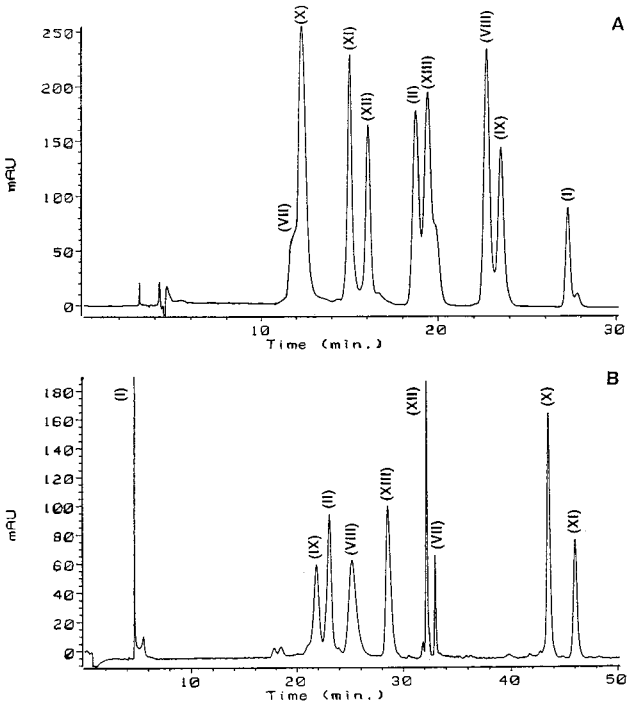

Figure 4. HPLC profiles of a mixture of purified standards of lycopene oxidation products prepared by partial synthesis: (A) separation on a C_{18} reversed-phase column with eluent A; (B) separation on a silica-based nitrile-bonded column with eluent B. For HPLC peak identification, see Figure 2. HPLC conditions are described in the text.

For a typical HPLC (eluent A) profile of carotenoids, including lycopene and its metabolites, in tomato paste, see the publication by Tonucci et al. (1995). Lycopene 5,6-epoxide in tomato and tomato products may be a precursor of rearranged epoxides **VIII** and **IX**, which may be formed due to the acidic nature of tomatoes as well as the processing conditions. Therefore, the natural occurrence of lycopene 5,6-epoxide in tomato products cannot be established with certainty.

In an earlier publication (Khachik et al., 1992a), we had misidentified the lycopene metabloite in human plasma as *all-E*-5,6-dihydroxy-5,6-dihydro-ψ,ψ-carotene, which was reported to be accompanied by a minute quantity of a mono-*Z*-isomer. However, recent examination of this isolated lycopene metabolite by HPLC (eluent E) has now revealed that this compound comprises two isomeric lycopene metabolites identified as

2,6-cyclolycopene-1,5-diol A and B (see Figure 2). These metabolites were separated by semipreparative HPLC (eluent E) and identified by comparison of their HPLC-UV−vis/MS profiles on a reversed-phase (eluent A) and a nitrile-bonded column (eluent E) with those of the reference samples of 2,6-cyclolycopene-1,5-diol A and B prepared by partial synthesis.

To ensure that the presence of lycopene metabolites in human serum was not an artifact of handling, extraction, and/or chromatography, a purified sample of lycopene was subjected to the same extraction procedure, solvents, and chromatographic methods employed for the extraction and analysis of human serum. Numerous experiments revealed that lycopene was quite stable under these conditions and did not undergo any structural transformation. In another experiment, exposure of purified lycopene to air for prolonged periods only resulted in degradation of this compound and according to HPLC (eluent A and B), 2,6-cyclolycopene-1,5-diols A and B were not formed.

Although epoxides **II**, **VIII**, and **IX** are present in tomato products and many foods, we have been able to detect diols **X** and **XI** only in human serum and milk (Khachik et al., 1997a). This is in agreement with our bioavailability and metabolic studies with carotenoids to date as well as a recent lycopene supplementation study involving humans, which confirm carotenoid epoxides, in general, are not absorbed (Khachik et al., 1995, 1997b; Paetau et al., 1997). In addition, epoxides **II**, **III**, and **IX** are sensitive to acids and may therefore undergo degradation or rearrangement to diols **X** and **XI** in an acidic stomach. Alternatively, these reactions may be catalyzed by certain enzymes. Another possible source for diols **X** and **XI** in human serum is the in vivo oxidation of lycopene followed by rearrangement and ring opening. Because compounds **X** and **XI** are found in the tomato products at low concentrations, only metabolic studies with lycopene labeled with a stable isotope, that is, ^{13}C, can establish the in vivo oxidation of this compound in humans. In view of the important biological activity of 2,6-cyclolycopene-1,5-diol (King et al., 1997), the total synthesis of this compound has recently been patented (Pfander and Traber, 1997).

Nomenclature. Many of the compounds prepared by partial synthesis in this paper are carotenoids with novel end-groups which have not been subjected to IUPAC nomenclature to date. To name these compounds, we have adopted the recommendations of Professor Conrad Hans Eugster (Department of Chemistry, University of Zurich, Switzerland), an internationally known authority and an expert on stereochemistry, structural elucidation, and chemistry of carotenoids. We have therefore designated the term 2,6-cyclolycopene to represent the novel five-membered ring end-group of lycopene epoxides that are formed by cyclization at C(2) and C(6). With this nomenclature, we have not altered the conventional numbering system of carotenoids. A similar approach has also been used with the other synthetic compounds reported here.

ACKNOWLEDGMENT

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