Efficient Total Synthesis of Lycophyll (ψ , ψ -Carotene-16,16'-diol)

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Abstract:

A practical procedure is described for the total synthesis of lycophyll (16,16'-dihydroxy-lycopene; ψ,ψ -carotene-16,16'-diol), based on a C10 + C20 + C10 synthetic methodology using the commercially available materials geraniol (C10) and crocetin-dialdehyde (C20). A late-stage double Wittig olefination on crocetindialdehyde was used to form the desired lycophyll scaffold in eight linear synthetic steps, while generating a mixture of polyenic geometric isomers that could be effectively separated using HPLC. All-*trans* lycophyll was subsequently separated to >95% purity by semipreparative chromatography using a C30 carotenoid column.

Introduction

Studies in cultured human cells¹⁻³ have shown that lycopene (ψ,ψ -Carotene; Figure 1), the primary carotenoid in tomatoes, can be growth inhibitory against transformed cells as well as normal prostatic epithelium, alone and/or in combination with other antioxidants (e.g., vitamin E). In animal studies, the results regarding protection against proliferation of transformed cells induced with various carcinogenic agents have been mixed;⁴⁻⁶ in the ferret, the most representative model in terms of absorption-distribution-metabolism-excretion (ADME) for humans, lycopene was in fact protective against cigarette-smoke-induced lung pathology.7 Epidemiological studies in humans clearly support an association between dietary consumption of lycopenecontaining food products and a lower risk of prostate cancer.8 Prospective, randomized clinical trials in humans also demonstrate improved indices of proliferation and oxidative stress across a range of oral doses in cancer patients (e.g., 2 mg/day to 30 mg/day).⁹⁻¹¹ Whether lycopene itself, or

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Figure 1. Chemical structures of lycopene, lycoxanthin, and lycophyll.

another phytochemical in tomato-based products, provides the efficacy suggested by epidemiological studies is currently unknown. Delivery of a highly potent radical scavenger to prostatic tissue, to restore or augment endogenous antioxidant levels, should be a promising area of current prostate cancer research.^{12,13}

Lycoxanthin (ψ , ψ -Caroten-16-ol) and lycophyll (ψ , ψ -Carotene-16,16'-diol) (Figure 1), isolated from the red berries of Solanum dulcamara, are C40 lycopene xanthophylls functionalized with primary hydroxyl groups. The carotenoids of the berries were first investigated by Zechmeister and Cholnoky in 1936.14 The originally proposed chemical structures of the xanthophylls, however, lacked complete assignment and required further studies that were realized in the early 1970s. Utilizing high-resolution mass spectroscopy and NMR, the regiochemistry of the hydroxyl groups was characterized.^{15,16} Absolute confirmation of both structures was obtained approximately one year later, with the total syntheses of lycoxanthin and lycophyll reported by Kjøsen and Liaaen-Jensen in 1972.17 The original total synthesis was based on a C10 + C20 + C10 synthetic paradigm, in part due to the commercial availability of C20

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Scheme 1^a



^{*a*} (a) SeO₂, 95% EtOH, reflux; (b) NaClO₂, NaH₂PO₄, Me₂C=CHMe, *t*-BuOH/H₂O; (c) K₂CO₃, MeOH/H₂O; (d) CH₃I, K₂CO₃, DMF/H₂O; (e) CBr₄/Ph₃P, THF, 0 °C; (f) Ph₃P, EtOAc.

Scheme 2^a



^a (a) LiOMe in MeOH, toluene, reflux; (b) DIBAL, THF, 0 °C.

dialdehyde (crocetindialdehyde). Up to the present, little additional chemical or biological information has accumulated in the primary literature for either compound.¹⁸

In the current study, the original synthetic design by Kjøsen and Liaaen-Jensen was used as a guide to generate lycophyll by total synthesis. Retrosynthetic analysis of the target xanthophyll revealed an efficient methodology utilizing the commercially available materials geranyl acetate, a protected form of geraniol (C10), and crocetindialdehyde (C20). The concise total synthesis of lycophyll was realized in eight synthetic steps (Schemes 1 and 2). Synthetic highlights include an endgame double-Wittig olefination that successfully formed the target C40 scaffold while generating a mixture of geometric isomers (Scheme 2). The isomeric mixture was then effectively deconvoluted to yield one primary target, all-*trans* lycophyll.

Previous work by us and collaborators have shown that targeted derivatization of carotenoids can successfully increase the aqueous dispersibility of the highly lipophilic natural scaffolds.^{19–23} These compounds have demonstrated

beneficial effects as direct aqueous radical scavengers;^{21,24,25} as myocardial salvage agents in experimental infarction models;^{26–29} and as cancer chemopreventive agents.^{30–33} The derivatives have shown increased utility as parenteral agents in these settings, as well as improved oral bioavailability in model animal studies.³⁴ Acquisition of lycophyll through total synthesis (Schemes 1 and 2) should facilitate the generation of water-dispersible lycophyll salts. Such derivatives will likely find application in those indications in which parenteral delivery of highly potent radical scavengers possessing the lycopene scaffold is necessary to achieve their intended purpose. Specifically, these compounds will be evaluated for efficacy in contemporary *in vitro* and *in vivo* cancer chemoprevention models.

Experimental Procedures

Synthesis of Lycophyll, General. Crocetindialdehyde (8) was obtained from SynChem, Inc. (Des Plaines, IL) as a brick-red solid and was used without further purification. Acetic acid 3,7-dimethyl-8-oxo-octa-2,6-dienyl ester $(2)^{35}$ was synthesized by literature procedures from commercially available geranyl acetate (1). All other reagents and solvents used were purchased from Acros Organics (Morris Plains, NJ) and Sigma-Aldrich (St. Louis, MO) and were used without further purification. All reactions were performed

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under a nitrogen atmosphere. All flash chromatographic purifications were performed on Natland International Corporation 230-400 mesh silica gel using indicated solvents. LC/MS (APCI and ESI + modes) data were recorded on an Agilent 1100 LC/MSD VL system; column, Zorbax Eclipse XDB-C18 Rapid Resolution (4.6 mm \times 75 mm, 3.5 μ m); temperature, 25 °C; flow rate, 1.0 mL/min; mobile phase (A = 0.025% TFA in H₂O, B = 0.025% TFA in acetonitrile). Gradient program (for intermediates 2–7): 70% A/30% B (start), step gradient to 50% B over 5 min, step gradient to 100% B over 1.3 min, hold at 100% B over 4.9 min. Gradient program (for intermediates 9, 10): 70% A/30% B (start), step gradient to 50% B over 5 min, step gradient to 98% B over 3.3 min, hold at 98% B over 16.9 min. All-trans lycophyll was obtained from crude material using a Waters 996 Photodiode Array detector, Millipore 600E System Controller, and Waters 717 Autosampler; column, YMC C30 Carotenoid S-5 (10 mm \times 250 mm, 5 μ m column); temperature, 25 °C; flow rate, 4.7 mL/min; mobile phase (A = methanol (MeOH), B = methyl-tert-butyl ether(MTBE)). Gradient program: 60% A/40% B (start), step gradient to 80% A over 1 min, hold at 80% A over 119 min. Fractions were collected from 55 to 66 min. Fraction analysis was performed on a YMC C30 Carotenoid S-5 (4.6 mm \times 250 mm, 5 μ m column). Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity INOVA 500 spectrometer operating at 500 MHz (megahertz) for proton NMR (1H NMR) and 125 MHz for carbon NMR (13C NMR). Chemical shifts are given in ppm (δ), and coupling constants, J, are reported in hertz (Hz). Electronic absorption spectra were recorded on a Cary 50 Bio UV-visible spectrophotometer.

8-Acetoxy-2,6-dimethyl-octa-2,6-dienoic Acid (3). To a solution of aldehyde 2 (19.5 g, 92.7 mmol) in 300 mL of tert-butyl alcohol was added 2-methyl-2-butene (98.0 mL, 925 mmol). To this was added a solution of sodium dihydrogen phosphate (NaH₂PO₄) (44.5 g, 371 mmol) in 300 mL of water. Sodium chlorite (NaClO₂) (33.6 g, 371 mmol) was added in several portions. The resulting mixture was rapidly stirred overnight at room temperature. Ethyl acetate (EtOAc) was added, and the aqueous layer was acidified to pH 3 by addition of 1 M HCl. The organic layer was separated, and the aqueous layer was extracted with EtOAc $(3 \times 200 \text{ mL})$. The combined organic extracts were washed with brine, dried over magnesium sulfate (MgSO₄), and reduced to dryness in vacuo. The crude product (27.4 g, 121 mmol, >100% yield) was used in the next step without further purification: ¹H NMR (CDCl₃) δ : 6.84 (t of q, J =7.25 Hz, J = 1.50 Hz, 1H, =CH), 5.34 (t of q, J = 7.00 Hz, J = 1.50 Hz, 1H, =CH), 4.56 (d, J = 7.00 Hz, 2H, $-CH_2O-$), 2.31 (q, J = 7.50 Hz, 2H, $-CH_2-$), 2.15 (t, J = 7.50 Hz, 2H, $-CH_2$ -), 2.03 (s, 3H, $-CH_3$), 1.81 (s, 3H, -CH₃), 1.70 (s, 3H, -CH₃). ¹³C NMR (CDCl₃) δ: 173, 171, 144, 141, 127, 119, 61.1, 37.8, 26.9, 20.9, 16.3, 11.9. LC/MS (ESI): m/z 249 [M + Na]⁺.

8-Hydroxy-2,6-dimethyl-octa-2,6-dienoic Acid (4). To a solution of acid 3 (20.0 g, 88.4 mmol) in 400 mL of methanol (MeOH) was added a solution of potassium

carbonate (K₂CO₃) (24.4 g, 177 mmol) in 100 mL of water. The resulting mixture was vigorously stirred overnight at room temperature. The reaction was cooled to 0 °C, methylene chloride (DCM) (200 mL) was added, and the aqueous layer was acidified to pH 3 with 1 M HCl. The organic layer was separated, and the aqueous layer was extracted with DCM (2×200 mL). The combined organic extracts were washed with brine, dried over MgSO4, and reduced to dryness in vacuo. The crude product (9.65 g, 52.4 mmol, 59% yield) was used in the next step without further purification: ¹H NMR (CDCl₃) δ : 6.86 (t of q, J = 7.25Hz, J = 1.50 Hz, 1H, =CH), 5.43 (t of q, J = 7.00 Hz, J =1.50 Hz, 1H, =CH), 4.16 (d, J = 7.00 Hz, 2H, -CH₂O-), 2.33 (q, J = 7.50 Hz, 2H, $-CH_2-$), 2.16 (t, J = 7.50 Hz, 2H, -CH₂-), 1.83 (s, 3H, -CH₃), 1.68 (s, 3H, -CH₃). ¹³C NMR (CDCl₃) δ: 173, 144, 138, 127, 124, 59.2, 37.8, 27.0, 16.2, 12.0. LC/MS (ESI): m/z 207 [M + Na]⁺.

8-Hydroxy-2,6-dimethyl-octa-2,6-dienoic Acid Methyl Ester (5). To a solution of acid 4 (20.1 g, 109 mmol) in 400 mL of dimethylformamide (DMF) was added a solution of K₂CO₃ (16.6 g, 120 mmol) in 80 mL of water. The resulting mixture was vigorously stirred for several minutes. To the mixture was added iodomethane (CH₃I) (7.50 mL, 120 mmol) via syringe. The resulting mixture was vigorously stirred overnight at room temperature. Water (400 mL) and EtOAc (400 mL) were added, and the aqueous layer was acidified to pH 3 by addition of 1 M HCl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×200 mL). The combined organic extracts were washed with water (3 \times 500 mL), saturated aqueous sodium bicarbonate (NaHCO₃), and brine and dried over MgSO₄. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (MeOH/ CH_2Cl_2 , 1:49) to afford methyl ester 5 as a clear oil (19.4 g, 90% yield): ¹H NMR (CDCl₃) δ : 6.72 (t of q, J = 7.50Hz, J = 1.50 Hz, 1H, =CH), 5.43 (t of q, J = 6.75 Hz, J =1.50 Hz, 1H, =CH), 4.16 (d, J = 7.00 Hz, 2H, -CH₂O-), 3.73 (s, 3H, $-CH_3$), 2.31 (q, J = 7.50 Hz, 2H, $-CH_2$ -), 2.15 (t, J = 7.50 Hz, 2H, $-CH_2$), 1.83 (s, 3H, $-CH_3$), 1.69 (s, 3H, -CH₃). ¹³C NMR (CDCl₃) δ: 169, 142, 138, 128, 124, 59.3, 51.7, 38.0, 26.8, 16.2, 12.4. LC/MS (ESI): m/z 221 [M + Na]⁺.

8-Bromo-2,6-dimethyl-octa-2,6-dienoic Acid Methyl Ester (6). To a 0 °C solution of alcohol 5 (12.9 g, 64.9 mmol) in 250 mL of anhydrous THF was added carbon tetrabromide (CBr₄) (23.8 g, 71.4 mmol) in several portions. The mixture was stirred for a few minutes, and then triphenylphosphine (Ph₃P) (18.7 g, 71.4 mmol) was added and the mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the resulting residue was suspended in diethyl ether (Et₂O). The suspension was filtered through a pad of Celite. After solvent removal under reduced pressure, the resulting crude product (contaminated with triphenylphosphine oxide (Ph₃PO)) was used directly in the next step: ¹H NMR (CDCl₃) δ : 6.61 (t of q, J = 7.50 Hz, J = 1.50 Hz, 1H, =CH), 5 47 (t of q, J = 8.00 Hz, J = 1.50Hz, 1H, =CH), 3.92 (d, J = 8.50 Hz, 2H, -CH₂Br), 3.63



Figure 2. Chromatogram of "crude" lycophyll (10) obtained using a C18 reversed-phase HPLC column (see text). Total lycophyll content (including *cis* and *trans* geometric isomers) >90% (as AUC).



Time (min)

Figure 3. Chromatogram of "crude" lycophyll (10) obtained using a C30 carotenoid column (see text). Total lycophyll content (including *cis* and *trans* geometric isomers) >90% as AUC. All-*trans* lycophyll, which elutes at 21.139 min (23.6% AUC), was further purified by semipreparative chromatography and its absolute configuration was confirmed by NMR (Figure 5).

(s, 3H, $-CH_3$), 2.22 (q, J = 8.00 Hz, 2H, $-CH_2-$), 2.10 (t, J = 8.00 Hz, 2H, $-CH_2-$), 1.75 (d, J = 1.00 Hz, 3H, $-CH_3$), 1.66 (d, J = 1.00 Hz, 3H, $-CH_3$). ¹³C NMR (CDCl₃) δ : 168, 142, 141, 128, 121, 51.4, 37.7, 28.8, 26.4, 15.7, 12.2.

(2,6-Dimethyl-8-octa-2,6-dienoic acid methyl ester)triphenylphosphonium Bromide (7). To a solution of bromide 6 (9.20 g, 35.2 mmol) in EtOAc (200 mL) was added Ph_3P (10.2 g, 38.8 mmol). The resulting mixture was



Figure 4. Through-space connectivities of 10 as measured by 1D NOE difference experiments. Each double-headed arrow represents a medium to strong NOE interaction and hence a corresponding though-space contact revealing the close spatial proximity of the two protons or groups of protons.

vigorously stirred for a few minutes, at which time an insoluble material began to oil out from the solution, adhering to the sides of the flask. The reaction solution was then decanted into a clean reaction vessel. This procedure was repeated every 5 to 10 min until no more oily insoluble residue was noted, at which time a white solid started to precipitate from the solution. The cloudy mixture was then stirred overnight at room temperature. The mixture was filtered, and the filter cake was rinsed with EtOAc and dried in vacuo to afford phosphonium salt 7 as a white solid (9.60 g, 52% yield). ¹H NMR (CDCl₃) δ : 7.88–7.84 (*m*, 6 arom. H), 7.79–7.75 (*m*, 3 arom. H), 7.68–7.64 (*m*, 6 arom. H), 6.51 (t of q, *J* = 5.00 Hz, *J* = 1.00 Hz, 1H, =CH), 5.10 (q, J = 7.00 Hz, 1H, =CH), 4.70 (d of d, J = 15.0, J = 8.00Hz, 2H, $-CH_2PPh_3Br$), 3.67 (s, 3H, $-CH_3$), 2.16 (q, J =7.00 Hz, 2H, $-CH_2$ -), 2.08 (t, J = 6.00 Hz, 2H, $-CH_2$ -), 1.70 (s, 3H, $-CH_3$), 1.35 (d, J = 4.00 Hz, 3H, $-CH_3$). ¹³C NMR (CDCl₃) δ: 168, 146, 141, 135, 134, 130, 128, 118, 109, 51.7, 38.2, 26.2, 24.5, 17.2, 12.4. LC/MS (ESI): m/z 443 [M]⁺.

Dimethyl ψ,ψ -**Carotene-16,16'-dioate (9).** To a solution of crocetindialdehyde (8) (0.810 g, 2.74 mmol) and 7 (4.30 g, 8.21 mmol) in toluene (100 mL) was added 1 M lithium methoxide (LiOMe) in MeOH (7.67 mL, 7.67 mmol) via syringe. The resulting mixture was refluxed for 24 h and cooled to room temperature, and then water (100 mL) was added. The organic phase was collected, extracted with water twice, and then dried over anhydrous Na₂SO₄. After filtration and removal of the solvent in vacuo, the resulting residue was purified by flash chromatography (EtOAc/toluene, 1:99) to afford dimethyl ester **9** as a red solid (1.15 g, 67% yield, as a mixture of geometric isomers). LC/MS (APCI): m/z625 [M + H]⁺.

 ψ , ψ -Carotene-16,16'-diol (Lycophyll) (10). To a solution of dimethyl ester 9 (1.14 g, 1.83 mmol) in anhydrous THF (100 mL) at 0 °C was added diisobutylaluminum hydride (DIBAL) (20% by wt. in toluene) (9.13 mL, 11.0 mmol) via syringe. The mixture was warmed to room temperature and stirred for 1 h. The reaction was guenched by the sequential addition of water (440 μ L), 15% aqueous NaOH (440 μ L), and water (1.10 mL). The resulting mixture was stirred for 30 min and then dried over anhydrous MgSO₄. The resulting slurry was filtered, and the solvent was removed in vacuo to afford the diol 10 as a red solid (1.01 g, 97% yield, as a mixture of geometric isomers). ¹H NMR (CDCl₃) δ : 6.63 (m, 4H), 6.48 (d of d, J = 15.0 Hz, J =11.0 Hz, 2H), 6.36 (d, J = 15.0 Hz, 2H), 6.26 (m, 4H), 6.19 (d, J = 11.5 Hz, 2H), 5.95 (d, J = 11.0 Hz, 2H), 5.40 (brt,J = 6.90 Hz, 2H), 4.00 (s, 4H), 2.19 (m, 4H), 2.16 (m, 4H),



1.97 (s, 12H), 1.82 (s, 6H), 1.68 (s, 6H). LC/MS (APCI): m/z 569 [M + H]⁺.

Results and Discussion

Following the original synthetic route utilized by Kjøsen and Liaaen-Jensen,¹⁷ our synthetic strategy was likewise based on the availability of crocetindialdehyde 8. The original synthesis utilized an endgame Wittig olefination using 2 molar equiv of C10 phosphonium salt for 1 equiv of C20 dialdehyde to form lycophyll's C40 scaffold. Significant synthetic effort involved the preparation of the required C10 head pieces. Kjøsen and Liaaen-Jensen's route toward the C10 fragment began with a three-carbon synthon involving nine synthetic steps that included two Wittig olefination coupling reactions. This methodology successfully produced the desired head piece in fair yield while also introducing significant amounts of cis-olefin contamination. Using the original route as a template, our efforts toward a concise and efficient preparation of lycophyll involved three key goals: (1) the development of a highly convergent synthesis of the target scaffold, (2) the preparation of an all-trans C10 headpiece, and (3) the optimization of synthetic manipulations needed to access multiple gram amounts of generated intermediates and the final target.

Geraniol, an abundantly available and naturally occurring C10 allylic alcohol, proved to be an appropriate starting synthon in preparing the synthetic intermediate phosphonium salt 7 (Scheme 1). Specifically, geranyl acetate 1 underwent regioselective oxidation using selenium dioxide to afford known aldehyde 2.35 The aldehyde was then cleanly oxidized to carboxylic acid 3 with $NaClO_2$ in the presence of 2-methyl-2-butene. Chromium-based oxidants such as pyridinium dichromate and Jones' reagent were screened, yielding a complex mixture largely contaminated with chromium-containing byproducts that proved difficult to remove. The acetate of 3 was saponified using K_2CO_3 in MeOH/H₂O to form the free allylic alcohol 4. Treatment of 4 with CH₃I converted the carboxylic acid to its corresponding methyl ester. Initially, the allylic alcohol of 5 was converted directly to the phosphonium salt using Ph₃P·HBr, however, in poor yield and with unacceptable amounts of cis-olefin contamination. A more mild, two-step protocol was adopted, such that the phosphonium salt was accessed through the preceding halide. Specifically, addition of CBr₄ and Ph₃P to alcohol 5 afforded bromide 6. The crude bromide was then treated with Ph₃P to provide the all-trans phosphonium salt 7 in good vield. NOE difference³⁶ experiments were utilized to confirm the trans-olefin geometry about bonds 2 and 6 of phosphonium salt 7. The Wittig condensation (Scheme 2) of phosphonium salt 7 with crocetindialdehyde 8 yielded dimethyl ester 9. Reduction of diester 9 with DIBAL provided lycophyll 10 (Figure 2) as a complex mixture of geometric isomers. Subsequent purification of the all-trans fraction (Figure 3) from the complex mixture was afforded by HPLC chromatography, yielding all-trans lycophyll at >95% purity (as area under the curve; AUC).

Table 1. ¹ H NMR Data of Lycopene ³⁷ and Lyco	ophyll
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	5 1	5 1 5
	lycopene	lycophyll
H-C(2) H-C(2')	5.11	5.40
2 H - C(3)	2.11	2.19
2 H - C(3) 2 H - C(4) 2 H - C(4)	2.11	2.16
2 H - C(4) H - C(6)	5.95	5.95
H-C(6') H-C(7)	6.49	6.48
$\begin{array}{c} H-C(7') \\ H-C(8) \end{array}$	6.25	6.25
H-C(8') H-C(10)	6.18	6.19
H-C(10') H-C(11)	6.64	6.63
H-C(11') H-C(12)	6.35	6.36
H-C(12') H-C(14)	6.25	6.26
H-C(14') H-C(15)	6.62	6.63
H-C(15') Me(16)	1.69	
Me(16') 2 H-C(16)		4.00
2 H–C(16') Me(17)	1.61	1.68
Me(17') Me(18)	1.82	1.82
Me(18') Me(19)	1.97	1.97
Me(19') Me(20)	1.97	1.97
Me(20')	1.77	1.77

Lycophyll (as both the mixture of geometric isomers as well as the purified all-*trans* form) has been subsequently utilized in *in vitro* and *in vivo* biological experiments

The all-trans configuration of the polyene chromophore and the regiochemistry of the primary hydroxyl groups of the purified material were subsequently confirmed by 2D COSY, 1D TOCSY, and NOE analysis. The connectivity of most of the coupled protons was deduced by a 2D COSY experiment. Using one-dimensional NOE difference experiments, through-space couplings confirmed the expected trans-orientation of selected polyenic protons (Figure 4). The chemical shifts and coupling constants of two sets of two overlapping olefinic protons (Figure 5) were revealed by a series of 1D TOCSY experiments. A comparison of polyenic ¹H NMR data of all-*trans* lycopene³⁷ with purified, synthetic all-trans lycophyll showed a near complete matching of peaks, specifically in ppm value, multiplicity, and integration (Table 1). As seen in Figure 6, the electronic absorption of lycophyll (as a mixture of cis/trans isomers) in various solvents displays the characteristic overall shape and fine structure expected of the lycopene chromophore. The positions of peaks I, II, and III in acetone (444, 469, and 499 nm) are slightly blue-shifted from those reported by Britton et al. (446 nm, 475 nm, 505 nm)¹⁸ for all-trans lycophyll

⁽³⁶⁾ Stotta, K.; Keelera, J.; Vanb, Q. N.; Shakab, A. J. J. Magn. Reson. 1997, 125, 302.

⁽³⁷⁾ Hengartner, U.; Bernhard, K.; Meyer, K.; Englert, G.; Glinz, E. Helv. Chim. Acta 1992, 75, 1848.



Figure 6. UV/vis spectral evaluation of lycophyll (as mixture of geometric isomers) in four solvents of differing polarities: hexanes, acetone, ethanol (EtOH), and tetrahydrofuran (THF). Concentration of lycophyll standardized to $1 \mu g/mL$ in each solvent. Ethanol and hexanes solvents included 0.5% THF. The absorbance in acetone is reported above 300 nm due to interference from absorbance of the solvent itself between 200 and 300 nm.

and is likely due to the presence of *cis* isomers in this spectral sample. As expected, as solvent polarizability increases, red-shifting of the absorbance spectrum is seen, nearly 8 nm for peak II between hexanes and THF.

Conclusion

In summary, we report the improved total synthesis of the rare xanthophyll lycophyll at gram scale, with methods for purification to desired geometric isomers using semipreparative chromatography. The natural tissue tropism of these compounds can now be exploited to introduce potent radical scavenging activity through additional methods of drug administration. As such, these compounds will likely find application in those therapeutic areas in which lycopenelike compounds have previously shown efficacy, such as prostate cancer.

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