180–185° for 45 min under mild aspirator vacuum, **9** furnished 3.34 g (75% yield from **7**) of 2,10-dimethyloctacosanoic acid (**10**) as a colorless, waxy solid: mp 49–51° (after crystallization from acetone); ir (CCl_4) 3500–2400 and 1712 cm^{-1} (carboxyl); ^1H NMR δ 12.30 (1 H, s, $-CO_2H$), 2.33 (1 H, m, >CHCO–); mass spectrum *m/e* (rel intensity) 452 (42, M^+), 143 (21), 130 (26), 97 (22), 87 (43), 74 (100, base), 71 (47), 69 (43), 57 (67), 43 (21). Anal. (vacuum sublimed sample). Calcd for $C_{30}H_{60}O_2$: C, 79.58; H, 13.36. Found: C, 79.77; H, 13.63.

3,11-Dimethyl-2-nonacosanone (1). Over a period of 45 min, 9.0 ml of 1.26 *M* methyllithium in ether was added under argon to a rapidly stirred solution of 2.50 g (5.53 mmol) of acid **10** in 35 ml of dry ether cooled to −10°. The mixture was stirred at −10 to −5° for 20 min and then at 25° for 4 hr, after which it was poured slowly, with stirring, into 100 ml of ice-cold 5% hydrochloric acid. Extraction with two 50-ml portions of ether followed by washing with 5% sodium bicarbonate, saturated sodium chloride, decolorization, drying, and evaporation yielded 2.25 g of colorless and nearly pure (by TLC and GLC) ketone **1**, which partially solidified at 25° (mp 24–28°). For purification, 2.20 g of this product was chromatographed on 150 g of silica (Mallinckrodt SilicAR CC-7). After elution with 200 ml of hexane, 1.91 g (78%) of purified **1** (homogeneous by TLC and GLC) was collected with 600 ml of 5% ether in hexane as a waxy solid with a very faint, thionyl chloride-like odor: mp 28–31° (lit.[4] 29–31°); ir (CCl_4) 1723 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) and ^{13}C NMR (Bruker HX-90, $CDCl_3$) spectra indistinguishable from those reported[2,4] for the natural pheromone; mass spectrum *m/e* (rel intensity) 450 (3, M^+), 85 (9), 72 (100, base), 71 (6), 69 (5), 57 (11), 55 (6), 43 (14). Anal. (after evaporative distillation, 0.5 mm). Calcd for $C_{31}H_{62}O$: C, C, 82.59; H, 13.86. Found: C, 82.81; H, 14.13.

The 2,4-DNP of **1** crystallized from methanol–ethyl acetate in fine yellow needle clusters, mp 56–62° (lit.[4] mp of natural pheromone 2,4-DNP, 55–56°). Anal. Calcd for $C_{37}H_{66}N_4O_4$: C, 70.43; H, 10.54; N, 8.88. Found: C, 70.20; H, 10.65; N, 8.89.

3-Methyl-2-heneicosanone (11) (with David J. Clymer). Under the same conditions used to prepare ketone **1** from acid **10**, 3.00 g (9.20 mmol) of 2-methyleicosanoic acid[11] [mp 60–61° (lit.[11] mp 61.5–62°)] in 125 ml of ether was allowed to react with 16.3 ml of 1.25 *M* methyllithium in ether to yield 2.44 g (78%) of chromatographed ketone **11**: mp 29–29.5°; ir (CCl_4) 1723 cm^{-1} (ketone); ^1H NMR δ 2.39 (1 H, m, J = 6.8 Hz, >CHCO–) 2.01 (3 H, s, CH_3CO–), 1.02 (3 H, d, J = 6.8 Hz, CH_3CHCO–); mass spectrum *m/e* (rel intensity) 324 (1.3, M^+), 85 (13), 72 (100, base), 57 (15), 55 (10), 43 (15), 28 (19). Anal. (after evaporative distillation, 0.5 mm). Calcd for $C_{22}H_{44}O$: C, 81.41; H, 13.66. Found: C, 81.38; H, 13.87.

The 2,4-DNP of **11** crystallized from ethanol in yellow spores, mp 77–78°. Anal. Calcd for $C_{28}H_{48}N_4O_4$: C, 66.63; H, 9.59. Found C, 66.68; H, 9.97.

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Registry No.—**1**, 53623-10-2; **1** 2,4-DNP, 56629-71-1; **2**, 25542-64-7; **3**, 34455-70-4; **4**, 56599-03-2; **5**, 56599-04-3; **6**, 56599-05-4; **7**, 55590-34-6; **9**, 56599-06-5; **10**, 56599-07-6; **11**, 56599-08-7; **11** 2,4-DNP, 56599-09-8; 2-methyleicosanoic acid, 56599-10-1.

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Synthesis of Aflatoxin Q_1

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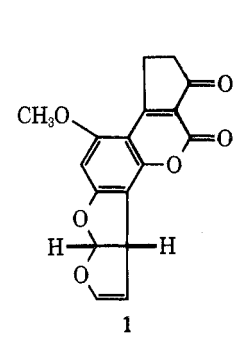
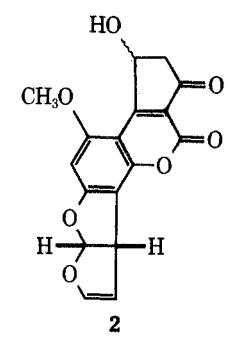
To interpret differences in susceptibility of various animal species to the carcinogenic effects of aflatoxin B_1 (**1**) a knowledge of its metabolic fate is of much importance.[1] The in vitro metabolism of the carcinogen by liver homogenates of duck, rat, mouse, monkey, and human has been investigated and a major, new metabolite called aflatoxin Q_1 (**2**) was isolated and identified structurally by three groups of investigators using monkey[2,3] and human liver.[4] To decide whether the hydroxylation of B_1 (**1**) represents an activation or a detoxification mechanism substantial quantities of Q_1 (**2**) are needed for physiological evaluation. We have developed two simple chemical methods which transform B_1 (**1**) to the metabolite Q_1 (**2**).



1



2

The presence of the enol ether function in the starting material **1** made most presently known methods unsuitable for direct hydroxylation and our efforts, accordingly, centered about oxidation of carbanions, derived from starting material by proton abstraction. Small, but detectable amounts of Q_1 (**2**) were formed by oxidation of B_1 (**1**) in *tert*-butyl alcohol solution with oxygen, *tert*-butyl hydroperoxide, or hydrogen peroxide in the presence of potassium *tert*-butoxide. Oxidation of a lithium diisopropylamide generated anion with MoO_5·Py·HMPA[5] afforded similar results. Substantial quantities of Q_1 (**2**) were produced when solutions of B_1 (**1**) in methylene chloride–methanol containing aqueous sodium hydroxide were exposed to either silver(II) or -(I) oxide. Efforts to replace silver oxide with copper(I) or -(II) species, manganese dioxide, and thallium(III) nitrate failed and as a result the reaction parameters of the silver oxide oxidation were examined in some detail with the more readily available model compound **3**.[6] Silver(I) oxide proved to be superior and gave the alcohol **5** in 38% yield while 17% of the starting material **3** was recoverable by chromatography. The structure of the alcohol **5** was determined by NMR spectroscopy and catalytic hydrogenation, proceeding with the consumption of 3 equiv of hydrogen, to 5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (**4**).

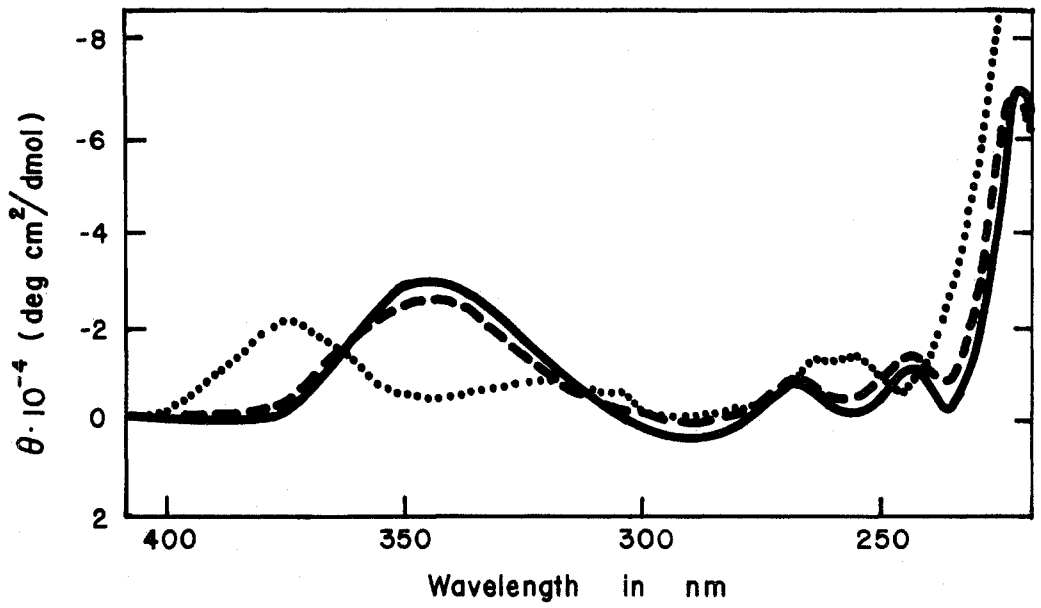
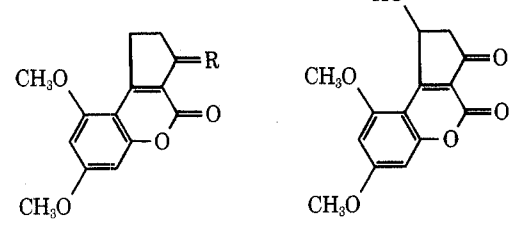


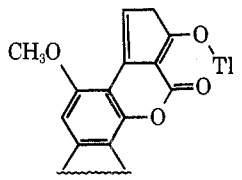
Figure 1. CD spectra of natural aflatoxin Q_1 (—), synthetic aflatoxin Q_1 (natural epimer – – –), and synthetic aflatoxin Q_1 (unnatural epimer · · · ·).

Oxidation of a thallium complex prepared from B_1 (1) and thallium(I) ethoxide[7] in methylene chloride–methanol with 95% hydrogen peroxide represents the most practicable synthesis of aflatoxin Q_1 (2). Excess hydrogen peroxide and 1 equiv of thallium(I) ethoxide at 0° afford optimal yield of both Q_1 (2) and the model compound 5. Oxidation



3, R = O
4, R = H_2

5



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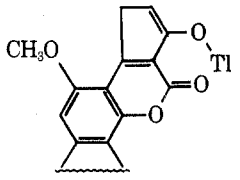

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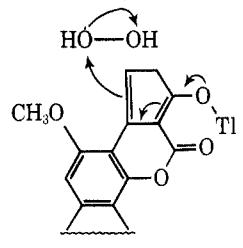

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is fast at the beginning but comes to a halt long before the starting material has been consumed and aqueous work-up leads to the recovery of as much as 50% of B_1 (1). Possibly two thallium enolates 6 and 7 are formed irreversibly. The less stable isomer 6 combines rapidly with hydrogen peroxide (arrows in 8) to produce Q_1 (2), with regeneration of the coumarin ring, while the more stable isomer 7 is transformed more slowly to hitherto unidentified, highly polar products.

Not unexpectedly chemical oxidation of B_1 (1) led to a mixture of two diastereomeric alcohols 2 (59% yield based on B_1 consumed) which was separated from starting material (56%) by chromatography. One aflatoxin Q_1 (2) epimer, mp 265° dec, identical with natural material, crystallized from methylene chloride–methanol–hexane in 41% yield. A second crystalline crop contained both epimers as revealed by the appearance of two acetal proton doublets at δ 8.5 in the NMR spectrum when measured in Me_2SO-d_6. After repeated chromatography of the remaining mother liquor the unnatural epimer, mp 235° dec, crystallized from the same solvent mixture. The proton spectra of the two epimers showed only small differences but circular dichroism (Figure 1) provided an easy means of differentiation. Conformational assignment to the secondary hydroxyl group will only be possible when a closely related alcohol of known configuration becomes available.

Experimental Section

Melting points are corrected. The following spectrometers were used: ir, Perkin-Elmer 247; ultraviolet, Perkin-Elmer 202 or Cary 14; NMR, Varian HA-100 or Hitachi Perkin-Elmer R-22 90 MHz; MS, Hitachi Perkin-Elmer RMU-6; CD, Cary 60.

Oxidation of Aflatoxin B_1 (1). A. Hydrogen Peroxide–Thallium(I) Ethoxide. To a solution of aflatoxin B_1 (1, 521 mg, 1.67 mmol) in 150 ml of methylene chloride at 0° a solution of thallium(I) ethoxide (382 mg, 1.54 mmol) in 38 ml of methylene chloride was added followed by a solution of 95–100% hydrogen peroxide (293 mg, 8.6 mmol) in 47 ml of methanol. After stirring at 0° for 47 hr the dark brown reaction mixture was filtered through a silica gel column (50 g) eluting with 500 ml of methylene chloride–methanol (3:1 v/v). The solvent was evaporated and the residue chromatographed (10 20 × 20 × 0.1 cm Analtech silica gel chromatoplates) eluting with chloroform–ethanol–hexane (10:2:1 v/v/v) to afford 293 mg (56%) of TLC-pure, crystalline aflatoxin B_1 (1) and 141 mg (26%) of TLC-pure mixture of epimeric aflatoxins Q_1 (2).

B. Silver(I) Oxide–Sodium Hydroxide. To a solution of aflatoxin B_1 (1, 100 mg, 0.32 mmol) in 53 ml of methylene chloride–methanol–water (27:22:4 v/v/v) at 0° silver(I) oxide (232 mg, 1 mmol) was added and then 1.2 ml of 0.5 *N* aqueous sodium hydroxide (0.6 mmol). After stirring at 0° for 160 min the mixture was filtered through a silica gel column (15 g) eluting with 200 ml of methylene chloride–methanol (3:1 v/v). The eluate was diluted with 350 ml of methylene chloride and extracted once with 4 *N* aqueous ammonium chloride and once with water. The organic

phase was diluted with 100 ml of dry benzene and evaporated to dryness. Chromatography (completely analogous to A) afforded 36 mg (36%) of the TLC-pure aflatoxin B_1 (1) and 32 mg (30%) of TLC-pure mixture of epimeric aflatoxins Q_1 (2).

Separation of Epimeric Aflatoxins Q_1 (2). A mixture of epimeric aflatoxins Q_1 (2, 341 mg, obtained mainly by procedure A) was dissolved in methylene chloride–methanol–hexane. Upon concentration 141 mg (41%) of the natural epimer crystallized as very fine needles in two crops. A third crystalline crop (98 mg, 29%) obtained from the same solvent mixture turned out to be a mixture (mainly unnatural epimer) of the two epimers as judged by the NMR spectrum in Me_2SO-d_6. The remaining mother liquor was rechromatographed twice [1. chromatography: 2 20 × 20 × 0.1 cm Analtech silica gel chromatoplates, eluted with chloroform–ethanol–hexane (10:2:1 v/v/v); 2. chromatography 2 20 × 20 × 0.1 cm Analtech silica gel chromatoplates, eluted with methylene chloride–ethyl acetate (2:1 v/v), R_f 0.15] to yield 55 mg of solid residue from which 38 mg (11%) of pure (as judged by the NMR in Me_2SO-d_6) unnatural epimer of aflatoxin Q_1 (2) crystallized from the solvent mixture used above. The two epimers showed the following physical properties.

Aflatoxin Q_1: mp 265° dec; uv max (100% C_2H_5OH) 223, 242 (sh), 267, 366 nm (ϵ 22250, 10800, 11800, 18700); uv min (100% C_2H_5OH) 252, 286 nm (ϵ 8600, 1000); ir ($CHCl_3$) 3600, 1780, 1710, 1640, 1610, 1575 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 329 (23), 328 (100, M^+), 313 (7), 312 (15), 310 (7), 299 (9); NMR, 90 MHz (Me_2SO-d_6) δ 2.21 (A part of ABX, 1, J_{AB} = 18, $J_{AX} \approx$ 1.5 Hz), 2.77 (B part of ABX, 1, J_{AB} = 18, J_{BX} = 6.5 Hz), 3.19 (s, H_2O from the solvent, exchanging with ROH of the substance), 3.85 (s, 3), 4.69 (d, 1, J = 7 Hz, of t, J = 2 Hz), 5.29 (t, 1, J = 2 Hz) overlapping with 5.38 (doubletoid m, X part of ABX, 1), 6.62 (t, 1, J = 2 Hz) overlapping with 6.65 (s, 1), 6.84 (d, 1, J = 7 Hz); CD (100% C_2H_5OH) 222, 236, 244, 255, 269, 290, 347 nm (θ −72200, −9500, −15300, −4100, − 10200, ±0, −26700), estimated absolute error in θ ±2500 deg cm^2/dmol.

Epiaflatoxin Q_1: mp 235° dec; uv max (100% C_2H_5OH) 224, 243 (sh), 267, 366 nm (ϵ 18200, 8400, 10000, 16500); uv min (100% C_2H_5OH) 252, 286 nm (ϵ 7300, 1200); ir ($CHCl_3$) 3600, 1775, 1710, 1635, 1605, 1575 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 329 (25), 328 (100, M^+), 326 (24), 313 (9), 312 (21), 310 (7), 299 (10); NMR, 90 MHz (Me_2SO-d_6) δ 2.24 (A part of ABX, 1, J_{AB} = 18, J_{AX} = 1.5 Hz), 2.80 (B part of ABX, 1, J_{AB} = 18, J_{BX} = 7 Hz), 3.23 (s, H_2O from solvent, exchanging with ROH of the substance), 3.86 (s, 3), 4.71 (d, 1, J = 7 Hz, of t, J = 2 Hz), 5.34 (t, 1, J = 2 Hz) overlapping with 5.41 (doubletoid m, X part of ABX, 1), 6.65 (t, 1, J = 2 Hz) overlapping with 6.68 (s, 1), 6.85 (d, 1, J = 7 Hz); CD (100% C_2H_5OH) 222, 244, 257, 292, 321, 345, 375 nm (θ −10600, −7200, −15500, ±0, −9600, −3000, −21500), estimated absolute error in θ ±2500 deg cm^2/dmol.

11-Hydroxy-5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (5) (Silver(I) Oxide–Sodium Hydroxide Reaction). To a stirred solution of 3 (26 mg, 0.1 mmol) in dichloromethane–methanol–water (11 ml, 4:4:1 v/v/v) in an ice bath was added in succession silver(I) oxide (70 mg, 0.3 mmol) and aqueous sodium hydroxide (0.5 ml, 0.4 *N*, 0.2 mmol). The reaction mixture was filtered through a silica gel column (6 g) after 2.5 hr, and the column washed with 250 ml of chloroform–methanol (3:1 v/v). The resulting solution was diluted with 500 ml of chloroform and washed once with 4 *N* aqueous ammonium chloride (300 ml) and once with distilled water (300 ml). The resulting organic phase was diluted with benzene (100 ml) and evaporated to dryness under reduced pressure. The residue was chromatographed (one 20 × 20 × 0.05 cm Analtech silica gel chromatoplate, chloroform–ethanol–hexanes, 10:2:1 v/v/v) to afford 3 (4.4 mg of a solid, R_f 0.73, 17% recovered) and 5 (10.2 mg of a solid, R_f 0.59, 46% based on amount of 3 reacted). Recrystallization of 5 from chloroform–ethanol–hexane gave pale yellow needles: mp 217–218°; ir (KBr) 3460, 2956, 1750, 1680, 1610, 1065 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 276 (M^+, 100), 260 (24), 245 (16), 233 (39), 205 (16), 69 (19); NMR (Me_2SO-d_6) δ 6.6 (AB pattern, 2, protons on C-6 and C-8), 5.45 (m, 1, proton on C-11), 3.96, 3.92 (two s, 6, $-OCH_3$), 3.32 (broad s, 1, –OH), 2.90 (d of d, 1, J = 6 and 18 Hz, C-9), 2.30 (d of d, 1, J = 2 and 18 Hz, C-9); uv max (100% C_2H_5OH) 216, 240 (sh), 248 (sh), 258 (sh), 357 nm (ϵ 23600, 13960, 13250, 11300, 27000).

11-Hydroxy-5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (5) (Thallous Ethoxide–Hydrogen Peroxide Reaction). To a solution of 3 (24.3 mg, 0.09 mmol) in dichloromethane (8 ml) in an ice bath was added a solution of thallous ethoxide (27.3 mg, 0.11 mmol) in dichloromethane (2 ml) and a solution of hydrogen peroxide (98%, 16.8 mg, 0.48 mmol) in methanol (3 ml). After 72 hr the reaction mixture was filtered through a silica gel column (6 g), and the column was washed with 300 ml of chloroform–methanol mixture (3:1 v/v). The resulting solution was evaporated and the residue chromatographed (one 20 × 20 × 0.05 cm Analtech silica gel chromatoplate, chloroform–ethanol–hexanes, 10:2:1 v/v/v) to afford 3 (13.6 mg, R_f 0.73, 56% recovered) and 5 (8.1 mg, R_f 0.59, 71% based on amount of 3 reacted).

Hydrogenation of 3. Compound 3 (4.8 mg, 0.0185 mmol) in absolute ethanol (6 ml) was hydrogenated in a Hösli microhydrogenator using a 10% Pd/C catalyst (30 mg) at 22° (730 mm). Hydrogen absorption was complete after an uptake of 0.91 ml (270 min). The catalyst was collected on a Celite filter pad and washed with chloroform. The combined filtrates were evaporated to dryness and the residue was chromatographed using a 0.25 mm silica gel thin layer chromatoplate (Analtech Co.) and chloroform–ethyl acetate (2:1 v/v) as the solvent. The major product, 5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (4, 3.5 mg, 77%), was located by visualizing under long wavelength ultraviolet light (pale blue fluorescence), and eluted off the silica gel with chloroform–methanol (3:1 v/v). Ir, uv, and melting point were identical with those of an authentic sample; MS (70 eV) *m/e* 246 (molecular ion); mp 183–184° after one recrystallization from ethanol. A mixture melting point with an authentic sample showed no depression. Uv max (C_2H_5OH) 248, 257, and 325 nm (ϵ 7700, 7000, 16100); ir ($CHCl_3$) 1706, 1608, and 1567 cm^{-1}.

Hydrogenation and Hydrogenolysis of 5. Compound 5 (4.6 mg, 0.016 mmol) in absolute ethanol (6 ml) was hydrogenated in a Hösli microhydrogenator using a 10% Pd/C catalyst (30 mg) at 22° (730 mm). Hydrogen absorption became very slow after an uptake of 1.0 ml (4.5 hr, 80% of theoretical value). The 5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (4) was isolated as described for the hydrogenation of 3, yield 3.2 mg (78%); ir, uv, and melting point identical with those of the authentic sample.

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Registry No.—1, 1162-65-8; 2 natural, 52819-96-2; 2 epimer, 56648-94-3; 3, 1150-42-1; 4, 1146-71-0; 5, 56599-31-6; thallium(I) ethoxide, 20398-06-5; silver(I) oxide, 1301-96-8.

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Geometric Isomers of 11,12-Dehydro-15-demethyl-β-axerophtene. New Geometric Isomers of Vitamin A and Carotenoids III[1]

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In connection with the photochemical studies of the polyenes in the vitamin A series,[3] we were in need of a complete set of geometric isomers of such a pentaene. The compound 11,12-dehydro-15-demethyl-β-axerophtene (I) was chosen because it has only four isomers and a procedure to the all-trans isomer is in the literature.[4] A modification of