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# Development of Synthetic Routes to D,L-α-Tocopherol (Vitamin E) from Biologically Produced Geranylgeraniol

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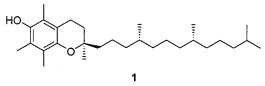
**Abstract:**

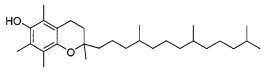
**The use of the biologically derived diterpene alcohol geranylgeraniol was explored as an alternative to petrochemical-based isophytol as a side-chain synthon for producing D,L-α-tocopherol. Two routes were studied, both of which begin with allylic epoxidation followed by olefin hydrogenation to give epoxyphytol. Epoxyphytol can be reduced with Red-Al to provide phytan-1,3-diol which upon acid-catalyzed condensation with trimethylhydroquinone gives vitamin E in fair yield. In a higher-yielding process, epoxyphytol was deoxygenated with methylrhenium trioxide/triphenylphosphine to generate a mixture of phytol and isophytol (>90% yield from geranylgeraniol). This mixture can serve as a "plug-in" replacement for isophytol in the final step of the currently practiced vitamin E chemistry. The use of methylrhenium trioxide to catalyse dehydration of vinyl dialkyl carbinols to 1,3-dienes was also demonstrated.**

## Introduction

Although the term vitamin E generally encompasses a number of homologues in the tocopherol and tocotrienol series, the most important member of the family is α-tocopherol.[1] This essential antioxidant is found in nature as the (2*R*,4′*R*,8′*R*)-isomer **1**, usually referred to as "D-α-tocopherol". Commercial production of **1** is carried out at about the 2000 tons/year level by processing soya oil deodorizer distillate for mixed tocopherols, followed by ring-methylating the lower homologues.[1,2] Despite the importance of **1** in human nutrition, the total synthesis of all-racemic α-tocopherol **2** has achieved greater commercial importance: Quantities approaching 20 000 tons/year of **2** are produced, largely for use in animal feeds.[2]

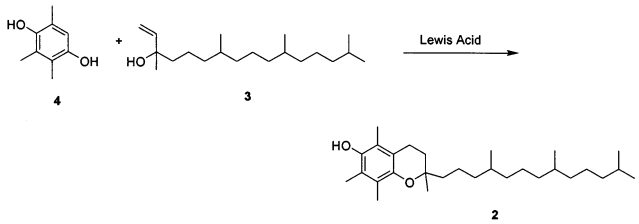


**1**



**2**

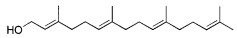
All commercially successful syntheses of **2** have relied on the Lewis acid-catalyzed reaction of isophytol **3** with trimethylhydroquinone ("TMHQ") **4**.[3−5] Different companies' all-*rac* vitamin E routes (the current most significant producers include Roche, BASF, Rhodia, and Eisai) generally vary mainly by the method used to obtain alcohol **3**. Although it is known that all-*rac* phytol **5** or phytadiene **6** can be used interchangeably with isophytol in the synthesis of **2**, synthetic expediency resulted in commercial dominance of isophytol as the side-chain synthon. The rather lengthy multistep continuous processes for **3** rely principally upon acetone, methanol, formaldehyde, acetylene, and isobutylene as starting materials.[1−3]




**4** **3** **2**

**5** **6**

It has recently come to our attention that a bio-based route to all-*rac*-α-tocopherol might be possible. Although for many decades the naturally occurring diterpene alcohol *trans,trans,-trans*-geranylgeraniol **7** was considered rare and inaccessible,[6,7] recent work indicates that both microbiological[8] and botanical[9,10] sources of **7** have the potential to achieve commercial feasibility. This report will describe work directed at utilizing compound **7** in the preparation of tocopherol **2**.



**7**

## Results and Discussion

The obvious route via direct condensation of **7** with TMHQ to produce a tocotrienol which could be reduced to **2** was shown to fail due to acid-catalyzed cyclization of the olefinic side chain prior or concomitant to the condensation with THMQ. Although some multistep routes which could in principle use **7** directly to produce a tocotrienol have been

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(1) Machlin, L. *Vitamin E: A Comprehensive Treatise*; Marcel Dekker: New York 1980.
(2) Netscher, T. In *Lipid Synthesis and Manufacture*; Gunstone, F., Ed.; Sheffield Academic Press: Sheffield, UK, 1999; pp 250−267.
(3) Parkhurst, R.; Skinner, W. In *The Chemistry of Heterocyclic Compounds*; Weissburger, A., Ed.; Wiley: New York, 1981; Vol. 36.
(4) Karrer, P.; Isler, O. U.S. Patent 2,411,967, 1946.
(5) Wehrli, P.; Fryer, R.; Metlesics, W. *J. Org. Chem.* **1971**, *36*, 2910.
(6) Ruzicka, L.; Firmenich, G. *Helv. Chim. Acta* **1939**, *22*, 392.
(7) Klinge, S.; Demuth, M. *Synlett* **1993**, 783.
(8) Millis, J.; Saucy, G.; Maurina-Brunker, J.; McMullin, T.; Hyatt, J. U.S. Patent 6,242,227, 2001.
(9) Jondiko, I.; Pattendon, G. *Phytochemistry* **1989**, *28*, 3159.
(10) Tan, B.; Foley, J. Int. Patent WO 00/71531 A1, 2000.


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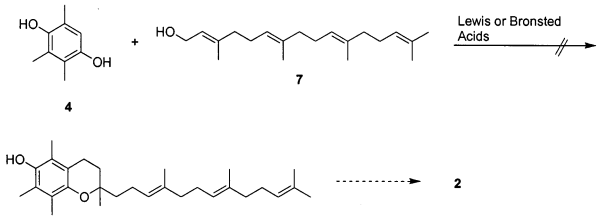
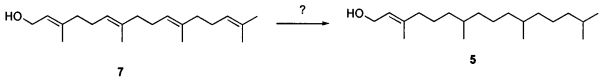
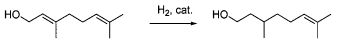
published, these processes are low-yielding and involve such problems as stoichiometric use of silver oxide.[11−13]



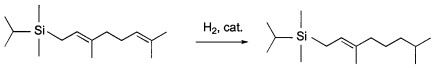

It thus becomes apparent that the basic problem in using geranylgeraniol **7** to make tocopherol **2** is that of selectively reducing **7** to phytol **5**:




A careful search of the literature failed to turn up any good precedent for such a hydrogenation. In fact, the only selective hydrogenations reported for polyprenyl systems analogous to **7** proceed in the opposite sense to what we required, as in the example reported by Calas et al:[14]



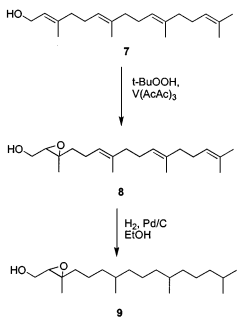

The only partial reduction reported to go in the direction we needed was reported by the same authors,[14] but this process was run on an allylsilane:




Since it was unclear to us whether this example worked as it did because of the electronics of the allylsilane group or the steric effect of the dimethylisopropylsilyl group, we examined at some length the hydrogenation of sterically hindered derivatives of **7**. The acetate, pivalate, *tert*-butyldimethylsilyl, and *tert*-butyldiphenylsilyl derivatives of **7** were prepared and subjected to catalytic hydrogenation over a number of catalysts (various supported Pt, Pd, Raney Ni, Co, and Cu, with and without catalyst poisons such as quinoline). In no case was any encouraging selectivity toward phytol formation observed. Often as many as 15−20 products were obtained (VPC analysis) due to *cis*/*trans* isomerization and olefin migration during the partial hydrogenations. Particularly discouraging was the fact that the same spectrum of products was obtained regardless of whether the acetate, pivalate, or silyl ethers were used. Therefore, we were forced to abandon hope of hydrogenating a geranylgeraniol derivative to phytol.

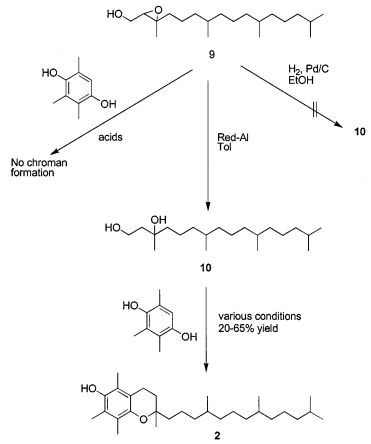
There remained a single published conversion of geranylgeraniol to phytol:[15] M. Julia and P. Roy added 3 mol of HCl to the nonallylic alcohol double bonds of **7** (−78 °C, pentane) followed by reduction of the tertiary chlorides with tributyltin hydride or zinc borohydride. We did not examine this route at the bench in view of its obvious cost and scale-up problems.

**Two Successful Approaches.** We have developed two routes to vitamin E from geranylgeraniol. Both routes begin with epoxidation[16] of **7** followed by catalytic hydrogenation of epoxide **8** to give epoxyphytol **9**.




When the epoxidation was carried out using a slight excess of a 3.3 M solution of *tert*-butylhydroperoxide in toluene and 1−2 mol % of vanadium acetonylacetonate catalyst in refluxing toluene, a nearly quantitative yield of epoxide **8** was obtained. Proton and $^{13}C$ NMR analysis of the crude product demonstrated the absence of epoxidation at any of the nonallylic alcohol olefins. Catalytic hydrogenation of **8** using 10−40 psi of hydrogen and 5% Pd/C catalyst in ethanol gave a nearly quantitative yield of **9** identical to a sample prepared by epoxidation of phytol.

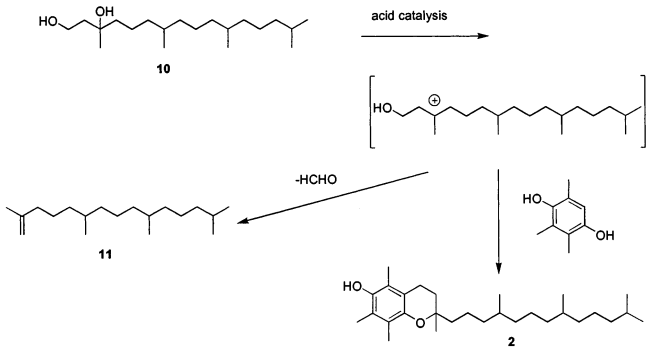
A number of attempts to use epoxide **9** in reactions with TMHQ to produce tocopherol or a hydroxytocopherol were made; in no case was any formation of chroman ring observed. When the epoxide was reduced with sodium bis-(2-methoxyethoxy)aluminum hydride in toluene, phytan-1,3-diol **10** was obtained in 95% yield. The structure of this diol was confirmed by comparison to literature data and by the fact that it formed a single monoacetate-monoalcohol upon acetylation with excess acetic anhydride in pyridine. Despite a number of attempts, we were unable to convert **9** to **10** by catalytic hydrogenolysis. In ethanol solvent, with and without acidic addenda, epoxide-opening occurred and ethoxylated phytantriols were obtained. In inert solvents (ethyl acetate, toluene) with Pd/C (or other catalysts), no reaction was seen even at 2500 psi $H_2$ and 150 °C for 8 h!




(11) Schudel, P.; Mayer, H.; Metzger, J.; Ruegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 2517.
(12) Svishchuk, A.; Vysotskaya, N. *Ukr. Khim. Zh.* **1975**, *41*, 506.
(13) Kajiwara, M.; Sakamoto, O.; Ohta, S. *Heterocycles* **1980**, *14*, 1995.
(14) Calas, R.; Pillot, J.; Dunogues, J. *C. R. Acad. Sci. Ser. 2* **1981**, *292*, 669.
(15) Julia, M.; Roy, P. *Tetrahedron* **1986**, *42*, 4991.

The use of diol **10** as a precursor to tocopherol has been reported previously. Blaha et al.[17] described the reaction of **10** (made by reduction of the Reformatsky product from phytone) with TMHQ catalyzed by a combination of $BF_3$ and zinc chloride to give a 90% yield of **2**. Sakamoto et al.,[18,19] working in a $^{13}C$-labeled series, obtained a 67% yield of **2** with *p*-TsOH catalysis in xylene. We have explored the reaction of diol **10** with TMHQ in considerable detail (well over 60 reactions were run), using many Lewis and protic acids catalysts alone and in combination in many solvents (acetic acid, glyme, nitrobenzene, toluene, THF, chlorobenzene, acetonitrile, nitropropane, and neat). Our best results came from using either nitrobenzene or acetic acid solvent with zinc chloride as catalyst. Reactions were quenched, and the crude tocopherol was analyzed by an HPLC quantitative method; in addition, in some runs the crude product was acetylated and the tocopheryl acetate quantified by an internal-standard VPC method. Analytical results using the two methods agreed to within 5%. Our best reproducible results had yields of about 60 to 65%. The typical figure was 64% based on diol or TMHQ (no advantage was seen to using either reactant in excess).

Thus, our results are consistent with those of Sakamoto et al.,[18] and we could not obtain the higher yield reported by Blaha.[17] After considerable work to account for the non-tocopherol products from this reaction, the reason for this became clear. Crude reaction products assaying 60−80 wt % tocopherol by HPLC or GC were found to contain a byproduct **11** which was not detected by HPLC (it did not absorb at the wavelength used) or VPC (the high-temperature method used to determine tocopheryl acetate caused **11** to emerge with the often high-boiling solvents present). Careful TLC analysis of the reaction mixtures showed the presence of a nonpolar component that usually migrated with the solvent front and was hard to visualize compared to tocopherol. Preparative TLC isolation followed by $^1H$ and $^{13}C$ NMR and mass spectral analyses proved that the byproduct was the $C_{19}$ olefin **11**, apparently formed by a *retro*-Prins reaction of diol **10**:

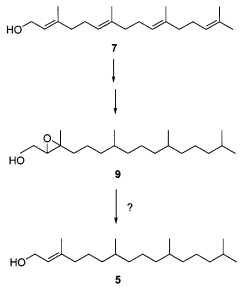



We are convinced that the 90% yield of tocopherol reported by Blaha et al. is in error: Olefin **11** is remarkably hard to detect, and even at levels as high as 20 wt % can go unnoticed in a proton NMR spectrum of tocopherol. It is unlikely that the techniques available to these workers in 1959 would have allowed its discovery. Thus, we obtained no evidence that the mixed $BF_3/ZnCl_2$ catalyst system employed by Blaha was advantageous.

Several attempts were made to overcome the yield-reducing formation of olefin **11**. This byproduct appeared with the use of any and all catalysts which led to the formation of tocopherol. Attempts to block the *retro*-Prins process by using the primary monoacetate of **10** in place of the free diol gave some improvement (70% yield of tocopherol with $ZnCl_2$ in refluxing acetic acid), but contamination by **11** was still a problem. Other conditions employed gave rise to double-bond position isomers of phytol and even a $C_{40}$ hydrocarbon dimer of phytol.

In summation of the route to tocopherol through diol **10**, there are two unsolved problems which would have to be overcome before commercial practicality is achieved: Formation of **10** by catalytic hydrogenation of epoxide **9** was not achieved, and the yield of tocopherol from **10** is limited by simultaneous cleavage to olefin **11**. Fortunately the discovery of a second, apparently superior, route to tocopherol from geranylgeraniol allowed us to put aside further work on the diol route.

**The Epoxide Deoxygenation Route.** Since the route from geranylgeraniol **7** to epoxyphytol **9** is high-yielding and inexpensive, an obvious approach to tocopherol would involve regeneration of phytol through reductive elimination of oxygen from **9**:



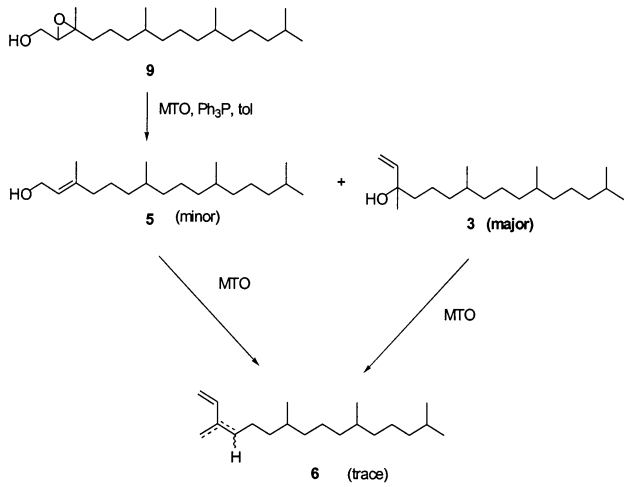

We initially chose not to explore this pathway because the known methods of epoxide deoxygenation (such reagents as chromous perchlorate,[20] magnesium amalgam,[21] and KSeCN[22] have been reported) did not appear commercially attractive. We were unable to reproduce a report that Zn/acetic acid "readily deoxygenates" aliphatic epoxides,[23] and prolonged heating of epoxyphytol with phosphines did not lead to any olefin formation.

This picture changed when the work of J. Espenson et al.[24] was noted. These workers reported that a catalytic amount of methylrhenium trioxide ($CH_3ReO_3$, "MTO") in

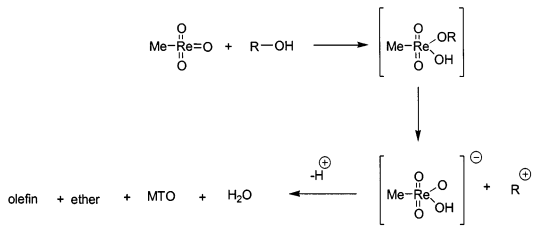
(16) Sharpless, K.; Michaelson, R. *J. Am. Chem. Soc*. **1973**, *95*, 6136.
(17) Blaha, L.; Hodrova, J.; Weichet, J. *Collect. Czech. Chem. Comm*. **1959**, *24*, 2023.
(18) Sakamoto, T.; Miyazawa, K.; Kajiwara, M. *Yukagaku* **1992**, *41*, 586.
(19) Kajiwara, M.; Sakamoto, O.; Katsura, H.; Ohta, S. *Heterocycles* **1981**, *15*, 1209.
(20) Kochi, J.; Singleton, D.; Andrews, L. *Tetrahedron* **1968**, *24*, 3503.
(21) Bertini, F.; Grasseli, P.; Zubieni, G. *J. Chem. Soc., Chem. Comm*. **1970**, 144.
(22) van Es, T. *Carbohydr. Res*. **1967**, *5*, 282.
(23) Sharpless, K. *J. Chem. Soc., Chem. Comm*. **1970**, 1450.
(24) (a) Zhu, Z.; Espenson, J. *J. Mol. Catal. A* **1995**, *103*, 87. (b) Zhu, Z.; Espenson, J. *J. Org. Chem*. **1996**, *61*, 324. (c) Abu-Omar, M.; Appelman, E.; Espenson, J. *Inorg. Chem*. **1996**, *35*, 7751.

hydrocarbon solvent transfers oxygen efficiently from simple epoxides (stilbene, cyclododecene, and tetramethylethylene oxides were used) to triphenylphosphine with the formation of olefin (79−87%) and triphenylphosphine oxide.

We immediately applied this method to epoxyphytol (toluene, 2 mol % MTO, 1.13 equiv $Ph_3P$) and were gratified to observe that although several products were produced all were usable as phytyl side-chain synthons in tocopherol synthesis. The major products were phytol **5** and isophytol **3** (ca. 1:2 ratio; both *E*- and *Z*-phytol present) in 80−83% yield; ca. 10% of a mixture of phytadienes **6** accompanied the alcohol products. Better results were obtained in refluxing toluene containing 1.00−1.04 equiv of triphenylphosphine and ca. 0.5 mol % of MTO for 2 h. Under these conditions the yield of phytol/isophytol isomers was 90.3% with only ca. 1% of olefins **6** present.

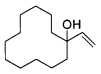
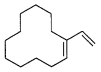
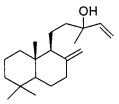
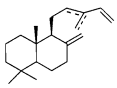
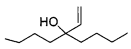
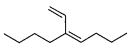



Control experiments established that the coproduction of both phytol **5** and isophytol **3** is due to interconversion of these allylic alcohols catalyzed by the methylrhenium trioxide catalyst. A recent patent[25] claims the use of MTO and related rhenium compounds to isomerize α-alkenols. However, the formation of the phytadiene mixture **6** appears to be novel. Control experiments proved that the diene mixture arose by dehydration of the isophytol product. Zhu and Espenson[24b] showed that MTO alone will dehydrate primary alcohols to form ethers. Low yields of olefins were slowly formed in some cases; no allylic alcohols were examined. These workers reasoned that the ether formation and dehydration reactions involved addition of alcohol to MTO followed by collapse of the hemiacetal-like adduct to a carbenium ion which undergoes proton elimination or reaction with alcohol to give organic products, water, and MTO:




Our results with epoxyphytol indicated that MTO alone in hydrocarbon solvents could convert vinyl carbinols to dienes rapidly in good yield, and a brief exploration of the reaction was undertaken. We found that when triphenylphosphine is present the dehydrating power of MTO is moderated and the catalyst largely functions to isomerize the starting alcohols.[26] A short series of dehydrations of vinyl carbinols to dienes was performed to establish the utility of MTO as a catalyst. These dehydrations were carried out by refluxing a 10% solution of vinyl carbinol in toluene containing 0.4−1.0 mol % of MTO for 2−4 h. Azeotropic removal of water was not necessary, and formation of a water layer was observed. The addition of MTO to the list of useful catalysts for this type of dehydration is justified on the bases of convenience (very little catalyst is required, and the MTO can be removed by extraction as perrhenate ion into a 5% aq $Na_2CO_3$ solution) and yield (in several cases, analogous *p*-TsOH/toluene dehydrations showed formation of complex product mixtures apparently due to further isomerization). Examples of this dehydration process are given in Table 1.

***Table 1:*** **Preparation of dienes from vinyl carbinols**[a]

| Entry | Carbinol | Diene | Yield |
|---|---|---|---|
| 1 |  |  | 76% |
| 2 |  |  | 93% |
| 3 |  |  | 69% |
| 4 |  |  | 64% |
| 5 |  |  | 61% |
| 6 |  |  | 76% |

[a] All reactions were carried out at 10% concentration in toluene in the presence of 0.4−1.0 mol % of MTO for 1−4 h at reflux. Yields are for distilled products. *E*/*Z* mixtures were obtained in entries 2, 4, and 6 (NMR).

The mixture of phytol, isophytol, and phytadienes from deoxygenation of phytol epoxide with MTO/$Ph_3P$ was found to cleanly produce tocopherol (82% yield) upon reaction with TMHQ with zinc chloride catalysis. Removal of triphenylphosphine oxide byproduct could be carried out at either the phytol/isophytol or the tocopherol stage. The yield of tocopherol was identical in our hands when either pure phytol, pure isophytol, or the mixture from the deoxygenation was used. Thus, we have demonstrated the conversion to geranylgeraniol to a tocopherol side-chain synthon in three steps, each of which proceeds in greater than 90% yield.

The formation of triphenylphosphine oxide as a byproduct in the deoxygenation is of concern. There exists proven

(25) Thorne, A.; Roeper, M.; Kneuper, H.-J. U.S. Patent 5,349,097, 1994.
(26) Hyatt, J. U.S. Patent 5,929,298, 1999.

technology for recycling $Ph_3PO$ back to $Ph_3P$,[27] but it would obviously be desirable to avoid this add-on process. We searched for a more economical oxygen acceptor but were not successful. Dimethyl sulfide in place of $Ph_3P$ gave no deoxygenation. The use of hypophosphorus acid was also studied. This gave acid-catalyzed epoxide ring-opening in aqueous systems and the use of sodium hypophosphite in water/alcohol mixtures afforded low yields of olefinic product accompanied by triols arising from epoxide reaction with water. Attempted phase-transfer reactions did not work.

Although the need to recycle triphenylphospine oxide remains an obvious place for improvement, the chemistry reported herein offers a promising new approach to vitamin E synthesis. Our conversion of bio-based geranylgeraniol to a tocopherol side-chain synthon in three steps is a radical departure from the conventional petrochemical-based multistep approach to isophytol yet allows a drop-in replacement in the final trimethylhydroquinone condensation. The valuable rhenium catalyst is quantitatively recoverable by extraction into dilute aqueous bases, where it forms the stable yellow perrhenate ion.[24] The use of the epoxide functionality to protect an olefin during reduction may prove to be a useful addition to synthetic methodology.

## Experimental Section

**General Methods.** $^1$H NMR spectra were recorded at 300 MHz on a Varian Gemini 300 instrument in $CDCl_3$ solvent with TMS internal standard. Spectra were re-recorded after a drop of $D_2O$ was added to all samples containing alcohols or phenols. Mass spectra were collected in field desorption mode on a Micromass Autospec magnetic double focusing instrument. Solvents and reagents were purchased from Sigma-Aldrich and were used as received.

**Geranylgeraniol-2,3-epoxide 8.** A solution of 5.0 g of all *trans*-geranylgeraniol **7** (0.0172 mol) in 20 mL of toluene was treated with 50 mg of vanadium tris(acetylacetonate) (0.8 mol %) and stirred under reflux in a nitrogen atmosphere. There was added dropwise 5.76 mL of 3.3 M *tert*-butylhydroperoxide in toluene (0.0190 mol). At the end of the addition, heating was discontinued, and the mixture allowed to cool to 23 °C. TLC analysis indicated complete conversion of the starting material to a single product. The mixture was treated with about 20 mL of 5% aqueous sodium bisulfite solution, stirred 10 min, and decanted, and the organic layer was washed (20 mL each) with water, 5% sodium bicarbonate solution, and brine, and dried over $MgSO_4$. Removal of solvent under vacuum afforded 5.28 g (98%) of pale yellow oily epoxide **7**. NMR: 5.2−5.05, m, 3H; 3.9−3.75, m, 1H; 3.65−3.75, m, 1H; 2.96, m, 1H; 2.2−1.95, m, 10H; 1.75−1.6, m, 12H; 1.6−1.4, m, 2H; 1.4−1.2, m, 3H. Mass spectrum: *m*/*z* 306 (calcd, 306). Anal: Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.11; H, 11.22.

**Epoxyphytol 9 from 8.** The crude product from an epoxidation performed as described above was dissolved in 50 mL of ethanol, treated with 0.20 g of 5% Pd/C catalyst, and hydrogenated (Parr apparatus) at 40 psi hydrogen and 40 °C for 4 h. The reaction mixture was vented, purged, filtered (Celite), and stripped of solvent to give 5.03 g (95%) of **9** as a colorless oil. NMR: 3.9−3.8, m, 1H; 3.75−3.65, m, 1H; 2.97, m, 4 lines, 1H; 1.7−1.0, br m, 21H; 1.30, s, 3H; 0.9−0.8, m, 12H. Mass spectrum: *m*/*z* 312 (calcd, 312).

**Epoxyphytol 9 from Phytol 5.**[28] A 3-L flask was charged with 100 g (0.337 mol) of phytol, 800 mL of *n*-hexane, and 0.9 g of $V(acac)_3$. The mixture was refluxed under nitrogen during the dropwise addition of 61.2 mL of 5.5 M (0.337 mol) *tert*-butylhydroperoxide in *n*-decane. The reaction mixture was cooled to room temperature and stirred overnight with 200 mL of 5% aqueous sodium bisulfite, and the organic phase then washed with water and brine, dried ($MgSO_4$), and stripped of hexane on the rotovap. Decane was then removed under gentle warming on the high-vacuum line to leave 97.2 g (92%) of **9** as a light yellow oil. NMR and mass spectra were identical to those of material prepared from geranylgeraniol.

**Phytan-1,3-diol 10.**[17] A 300-mL flask was charged with 11.3 g (0.036 mol) of epoxyphytol **9** and 100 mL of dry toluene. The mixture was stirred under argon at 0 °C during the addition of 17.4 mL of Aldrich Red-Al (65% Na bis(2-methoxyethoxy)aluminum hydride in toluene; 0.038 mol). The reaction was allowed to warm to 22 °C over 4 h, at which time TLC analysis of an acidified sample disclosed the formation of a single polar product. The reaction was cooled to 5−10 °C and quenched by addition of 50 mL of 2-propanol. Acidification with 5% aqueous HCl was followed by phase separation and washing of the organic layer with water (3 × 100 mL) and brine (1 × 100 mL) and drying over $MgSO_4$. Removal of solvent under vacuum left 10.6 g (93%) of **10** as a pale yellow viscous syrup. (Other runs gave yields as high as 97%; the average was 95%). NMR: 3.87, d of t, 2H; 1.8−1.0, br m, 23H; 1.24, s, 3H; 0.9−0.8, m, 12H. Mass spectrum: *m*/*z* 314 (calcd, 314). Acetylation of a sample of **10** (excess acetic anhydride, pyridine, 0−20 °C, 4 h) gave a 91% yield of a single monoacetate: NMR: 4.23, t, 2H; 2.07, s, 3H; 1.72−1.00, complex m, 23H; 1.22, s, 3H; 0.9−0.8, m, 12 H. Mass spectrum: *m*/*z* 356 (calcd, 356).

**α-Tocopherol 2 from Diol 10.** A solution of 1.20 g (0.0079 mol) of trimethylhydroquinone and 0.80 g (0.0059 mol) of anhydrous zinc chloride in 9 mL of glacial acetic acid was stirred under argon at reflux. To this was added dropwise a solution of 2.70 g (0.0086 mol) of phytandiol **10** in 5 mL of acetic acid and the solution refluxed 16 h. There was then added 5 mL of acetic anhydride and the mix refluxed a further 3 h. Workup by aqueous drownout, extraction with ethyl acetate, washing with 5% aqueous $NaHCO_3$, water, and brine, and drying ($MgSO_4$) followed by removal of solvent left 3.92 g of a dark oil which assayed 54 wt % α-tocopheryl acetate by internal standard VPC analysis. Yield of tocopherol, 60%.

Various modifications of this reaction using different stoichiometry, addition of cocatalysts and use of different Lewis acids, different solvents, and so forth gave yields of tocopherol in the 55−65% assay range. TLC analyses indicate

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the presence of a nonpolar byproduct which was isolated by preparative TLC and identified as olefin **11**: NMR: 5.09, br t, 2 H; 2.1−1.0, complex m, 24H; 0.9−0.8, m, 12H. GC/MS, *m*/*z* 266 (calcd, 266).

**Preparation of a Phytol/Isophytol/Phytadiene Mixture from Epoxyphytol 9.** A solution of 5.0 g of epoxyphytol **9** (0.016 mol) and 4.72 g of triphenylphosphine (0.018 mol) in 50 mL of toluene was treated with 0.080 g of methylrhenium trioxide (0.00032 mol) and stirred under reflux for 2 h. TLC analysis indicated the absence of **9** and formation of isophytol **3**, phytol **5**, and a small amount of front-running nonpolar product (dienes **6**). The mixture was cooled, filtered through a pad of silica gel to remove catalyst and triphenylphosphine oxide, and stripped of solvent to give 5.0 g of crude product mixture. Silica gel flash chromatography afforded 0.4 g of phytadienes **6** (7.4%) with spectral properties consistent with published data[29] and 3.9 g (83%) of a 3/1 mixture of isophytol **3** and (*E*/*Z*)-phytol **5** (VPC comparison with authentic materials).

**Larger-Scale Preparation of Phytol/Isophytol from Epoxyphytol 9.** A solution of 22.5 g (0.072 mol) of epoxide **9** and 19.7 g (0.075 mol) of triphenylphosphine in 200 mL of toluene was treated with 0.130 g (0.00052 mol) of methylrhenium trioxide and stirred under reflux for 3 h, by which time TLC indicated complete conversion. The reaction mixture was cooled and extracted twice with 50 mL of 5% aqueous sodium carbonate solution. The resulting yellow aqueous perrhenate solution was separated and the organic phase washed with water and with brine. The resulting solution was stripped of toluene to give a semisolid residue which was extracted with 100 mL of hexane, and the insoluble triphenylphosphine oxide was filtered off. The filtrate was thrice partitioned between 100 mL each of hexane and 2:1 methanol:water to remove further $Ph_3PO$. The hexane phase was dried ($MgSO_4$) and passed through a small pad of silica gel to remove final traces of triphenylphosphine oxide. After solvent removal under vacuum there was obtained 19.25 g (90.3%) of nearly colorless oily product. VPC and NMR analyses indicated the material to be composed of a 2.7/1 mixture of **3** and **5**, accompanied by less than 1% each of diene mixture **6** and triphenylphosphine.

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**α-Tocopherol 2 from Epoxyphytol 9.** A solution of 31.2 g (0.10 mol) of epoxyphytol **9** and 26.2 g (0.10 mol) of triphenylphosphine in 200 mL of toluene was treated with 0.20 g (0.00080 mol) of methylrhenium trioxide, and the resulting solution refluxed for 3 h. The mixture was cooled to room temperature, extracted (2 × 50 mL) with 5 wt % $Na_2CO_3$ aqueous, dried over sodium sulfate, and the toluene was removed on the rotovap. The resulting semisolid mixture of **3**, **5**, and triphenylphosphine oxide was dissolved in 50 mL of acetic acid.

A solution of 15.2 g (0.10 mol) of trimethylhydroquinone and 6 g (0.044 mol) of anhydrous zinc chloride in 150 mL of acetic acid was prepared, and the above acetic acid/**3**/**5** solution was added. The resulting mixture was stirred under reflux in an argon atmosphere for 2 h, cooled to room temperature, and drowned into 1 L of water. Extraction with hexane gave a crude product solution which was washed with 5 × 100 mL of 2/1 methanol/water, dried, and filtered through about 50 g of silica gel. Solvent removal under vacuum gave 41.73 g of yellow syrup which assayed (HPLC) 83.0 wt % **2**. Yield of **2** based on **9**, 80.5%.

**Diene Preparation by MTO Dehydration of Vinyl Carbinols.** The preparation of 1-vinylcyclododecene is typical. A solution of 1.20 g (0.0057 mol) of 1-vinylcyclododecanol in 10 mL of toluene was treated with 20 mg (0.08 mmol) of methylrhenium trioxide and stirred under reflux for 4 h. The mixture was cooled, extracted with 2 × 10 mL each of 5% aqueous $Na_2CO_3$, water, and brine. After drying ($Na_2SO_4$) and solvent removal there was obtained 1.02 g (93%) of an oily mixture of (*E*)- and (*Z*)-1-vinylcyclododecene whose spectral properties were in excellent accord with those of published data.[30]

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