Cationic Cyclization of a Substrate Having an Internal Acetylenic Bond. Synthesis of Euphol and Tirucallol[1]

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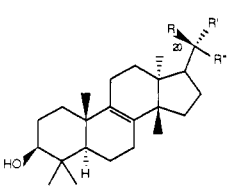
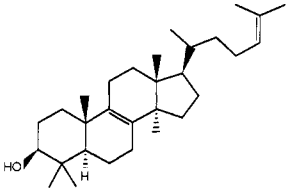
New methodological studies directed toward the synthesis of tetracyclic triterpenoids bearing the 8,9-olefinic bond involve the acid-catalyzed cyclization of the dienediynol **9** as the key step. Surprisingly the ring closure, giving mainly **10**, leads to the euphane rather than the lanostane ring system (see Scheme I). This discovery has made possible the first synthesis of euphol as well as its C-20 epimer tirucallol. New methodology was developed for the highly stereoselective production of tetrasubstituted olefinic bonds during the synthesis of the pro-C-13,14 olefinic bond of cyclization substrate **9** (Scheme II). The constitution of ketone **10** was established by conversion into the dione **30** as shown in Scheme III. This racemic material was rigorously identified with the natural enantiomer, prepared by degradation of euphol. Dione *l*-**30**, obtained by degradation of the natural product was used for reconstruction of the C-17 side chain to give euphol (**1a**) and tirucallol (**1c**); thus a formal totally synthetic pathway to these products has been established.

The cationic cyclization of a substrate with an internal acetylenic bond as in formula **9** has the potential of yielding, in one step, a tetracyclic ring system with an olefinic bond at 8,9 (steroid numbering) as found in many of the tetracyclic triterpenoids such as lanosterol and euphol. The present work discloses a study of this novel kind of cyclization and its application to the synthesis of euphol and tirucallol.

The tetracyclic triterpenes of the euphane class are distinguished from the lanostanes by inversion of the stereochemistry of carbons 13, 14, and 17 (compare formulas **1** and **2**). The compounds euphol (**1a**), euphorbol (**1b**) and tirucallol (**1c**), isolated from the resinified latex of *Euphorbium* species, are illustrative of the class.[2] The literature contains no report to date of a successful synthetic route to the euphane ring system. Recently, Kolaczkowski and Reusch reported[3] their progress on a conceptually short synthesis of butyrospermol (the 7,8-olefinic isomer of euphol), which was thwarted when the 5-epi compound could not be converted to the A/B trans ring fusion found in the euphanes.

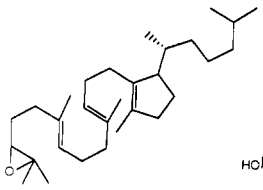




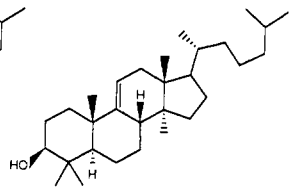
1a: R = H, R′ = CH_3
R″ = $(CH_2)_2CH{=}C(CH_3)_2$: euphol
b: R = H, R′ = CH_3
R″ = $(CH_2)_2C(=CH_2)CH(CH_3)_2$: euphorbol
c: R = CH_3, R′ = H
R″ = $(CH_2)_2CH{=}C(CH_3)_2$: tirucallol

2: lanosterol

The synthesis of the lanostanes has met with greater success. The Woodward–Barton formal total synthesis[4] of lanosterol (**2**) is well known. Also, in a nonenzymic polycyclization study reported[5a] by van Tamelen and coworkers it was shown that epoxides **3a,b** were converted with acid to a mixture that included dihydroprotolanosterol, isoeuphenol, 24,25-dihydroparkeol (**4**), and isotirucallenol. However, no compounds with the euphane nucleus were reported in the product of this cyclization reaction nor in other related cyclization studies.[5b]



3a,b (C-3 epimers)



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The plan for the present study was based on the known[6] stereoselective cyclization of trienynol **5** to form the steroidal product **6**, which was then readily converted in two steps to *dl*-progesterone. Furthermore, model studies performed by Michael E. Hendrick[7] showed that the

(1) This paper is part of the series on "biomimetic polyene cyclizations". For recent publications in this area, see: (a) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517–2518. (b) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852–5853.

(2) Ourisson, G.; Crabbé, P.; Rodig, O. R. *Tetracyclic Triterpenes*; Holden-Day: San Francisco, 1964.

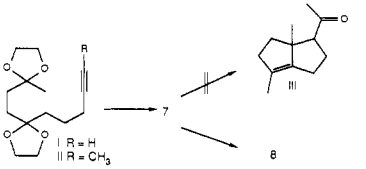
(3) Kolaczkowski, L.; Reusch, W. *J. Org. Chem.* **1985**, *50*, 4766.

(4) Woodward, R. B.; Patchett, A. A.; Barton, D. H. R.; Ives, D.; Kelley, R. *J. Am. Chem. Soc.* **1954**, *76*, 2852; *J. Chem. Soc.* **1957**, 1131.

(5) (a) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225–8228. (b) van Tamelen, E. E.; Murphy, J. W. *Ibid.* **1970**, *92*, 7204. (c) van Tamelen, E. E.; Freed, J. H. *Ibid.* **1970**, *92*, 7207.

(6) (a) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274–4282. (b) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *Ibid.* **1980**, *102*, 7800–7802.

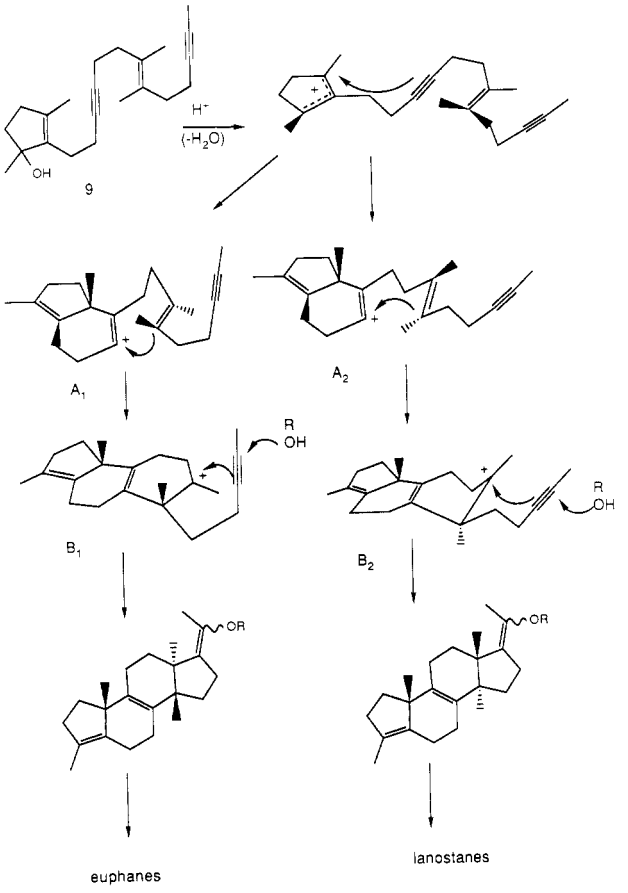
(7) The model cyclopentenol substrate **7** was prepared from the known[8] bis-ketal acetylene I by alkylation of its lithio derivative with methyl iodide to give II, followed by the hydrolysis–cyclodehydration sequence as described for the conversion of **21** to **23** and then treatment of the resulting cyclopentenone with ethereal methyllithium. Cyclization of **7** with trifluoroacetic acid and ethylene carbonate in methylene chloride at 0 °C for 1.5 h gave, after base treatment, a yellow oil, which showed absorption in the infrared spectrum at 5.85 μm, indicating the ketonic nature of the product. The ^1H NMR spectrum showed absorptions at δ 1.05 (s, 3 H), 1.00 (d, 3 H, *J* = 6 Hz), 0.90 (d, 3 H, *J* = 5 Hz), and 0.82 (s, 3 H), which could be accounted for by two angular methyl singlets and two ring methyl doublets of a pair of six-membered ring ketone stereoisomers **8**. Furthermore, there was no distinct singlet absorption at δ 2.2, indicating that this substance was not the methyl ketone III.



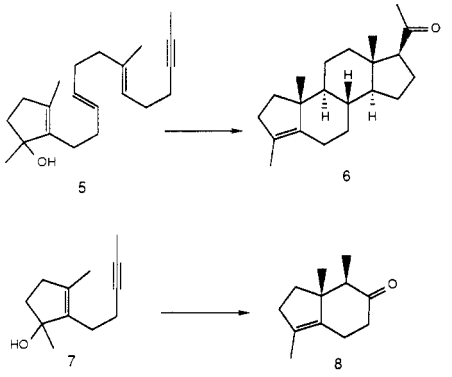
(8) Johnson, W. S.; Escher, S.; Metcalf, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1039–1041.

0022-3263/90/1955-2215$02.50/0

Scheme I



substrate **7** underwent cyclization to give **8** with the six- instead of the five-membered B ring.

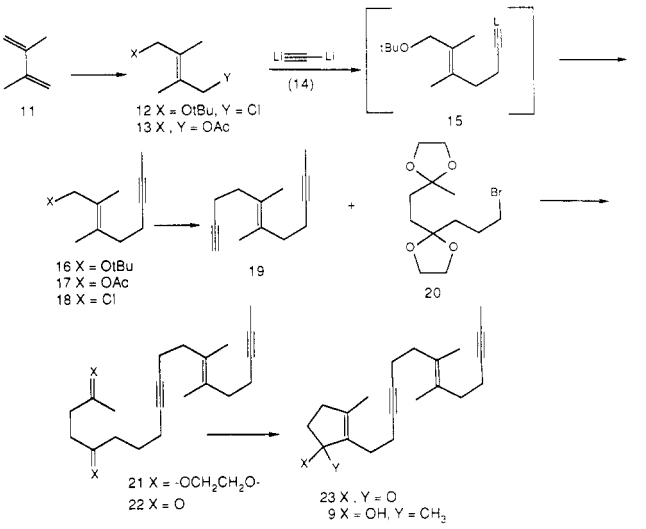


Accordingly, we proposed that dienediynol **9** might be expected to cyclize to form the six-membered ring vinyl cation A,[9] which could cyclize further to produce cation B_1 or B_2, depending upon the direction of attack of the tetrasubstituted olefin upon vinyl cation A (i.e., conformation A_1 or A_2 in Scheme I). Nucleophilic trapping of the vinyl cation produced upon anti attack of the acetylenic bond in cation B_1 would give the euphane skeleton, while cation B_2 would lead to the lanostane nucleus. Subsequent modification of ring A and elaboration of the side chain would yield compounds of the euphane or lanostane classes of tetracyclic triterpenes respectively.

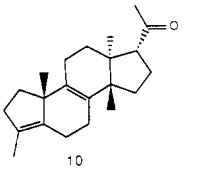
The present paper describes the synthesis of the bis-acetylenic substrate **9** and the study of its acid-catalyzed

(9) This analysis, although made as though the cyclization is a stepwise process, is not meant to imply any mechanistic preference. The partially cyclized cationic species may be regarded as a contributor to the transition state of a concerted process.

Scheme II



cyclization. Fortunately, the major tetracyclic product proved to be substance **10** with the euphane configuration. Refashioning ring A of **10** gave racemic dione **30** (Scheme III), which was unequivocally identified with the natural enantiomer, *l*-**30**, prepared by degradation of euphol. Dione *l*-**30**, obtained by degradation of the natural product, was used as a relay point for reconstruction of the C-17 side chain to give euphol (**1a**) and tirucallol (**1c**), thus providing the first totally synthetic pathway to these natural products.



Synthesis of the Cyclization Substrate. The substrate for cyclization, dienediynol **9**, was synthesized as outlined in Scheme II. Thus, when 2,3-dimethyl-1,3-butadiene (**11**) was treated in the cold with *tert*-butyl hypochlorite according to methodology developed with isoprene,[10] an 8:3 mixture of the corresponding 1,4- and 1,2-adducts was obtained. Careful fractional distillation gave the required 1,4-adduct **12** in 15–20% yield. The configuration of the newly formed olefinic bond was shown by conversion of **12** to the known[11] *trans*-allylic diacetate **13** under conditions that would not be expected to cause geometrical isomerization of the olefinic bond. Spectral data (IR and ^{1}H NMR) and VPC coinjection experiments showed that **13** contained less than 2% of the *cis*-diacetate.

The allylic chloride function of **12** was used to develop the methylacetylenic terminating group. The propargyl group was introduced, using the method of Hooz and Calzada,[13] by treatment of substance **12** with the dianion of propyne (**14**), generated from allene and 2 molar equiv

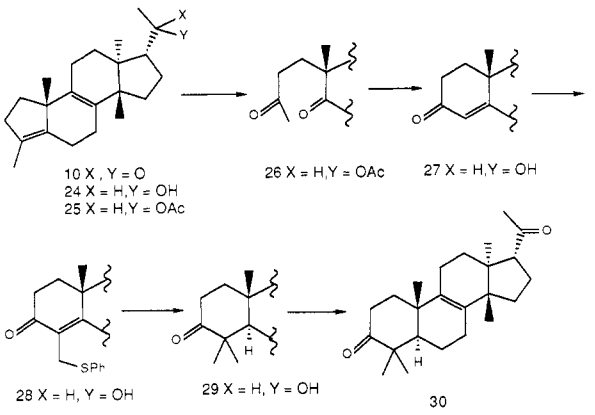
(10) Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608–4613.

(11) Conversion of the chloroether **12** into *trans*-2,3-dimethyl-2-butene-1,4-diol diacetate (**13**) was effected by treatment of **12** with sodium acetate in HMPA to give the corresponding ether acetate, followed by treatment with ferric chloride and acetic anhydride using a modification[12] of the published procedure.[10] Authentic specimens of the cis and trans diacetate were prepared according to Sweeting, O. J.; Johnson, J. R. *J. Am. Chem. Soc.* **1946**, *68*, 1057–1061.

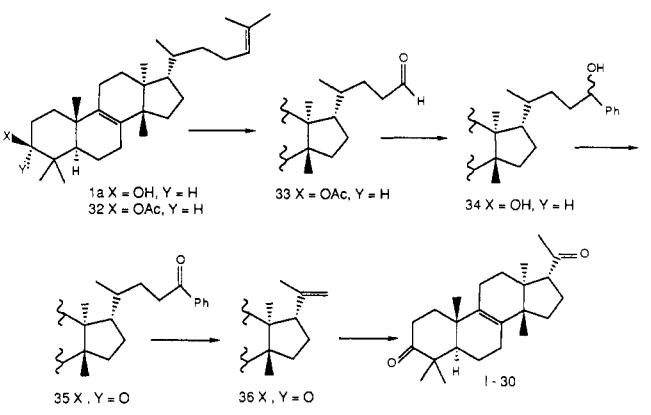
(12) Small, V. R.; Ganem, B. *J. Org. Chem.* **1974**, *39*, 3728–3730.

(13) Hooz, J.; Calzada, J. G.; McMaster, D. *Tetrahedron Lett.* **1985**, *26*, 271–274.

Scheme III



Scheme IV



of *n*-butyllithium at −20 °C. The resulting lithium acetylide **15** was treated with methyl iodide, leading directly to the ether **16** in 85% yield.

While examining the conversion[11] of ether **16** to acetate **17** using ferric chloride and acetic anhydride, we discovered, quite unexpectedly, mixtures containing the allylic chloride **18**. An effort was then made to develop conditions using acetyl chloride, ferric chloride, and carbon tetrachloride, which gave exclusively the allylic chloride **18** in 80% yield. Treatment of chloride **18** with the dianion of propyne (**14**), as described[13] above, except that an aqueous quench of the acetylide was used, gave the required enediyne **19** in 78% yield.

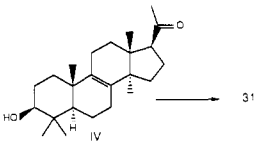
The convergent step in the synthesis of substrate **9** involved the alkylation of the anion of enediyne **19** with the known[14] bromide **20** to afford the bis-ketal **21** in 84% yield. Conversion of the bis-ketal to the cyclopentenol A ring of substrate **9** was accomplished as follows. Hydrolysis of bis-ketal **21** was effected in quantitative yield, using pyridinium tosylate in 12% aqueous acetone to give dione **22**, which was converted in 96% yield to cyclopentenone **23** with 1% sodium hydroxide in aqueous methanol. Cyclization substrate **9** was obtained in quantitative yield upon treatment of an ethereal solution of enone **23** with methyllithium. The synthesis of the cyclization substrate was thus accomplished in 34% overall yield (>96%, 1 product by VPC analysis) from chloroether **12**.

Cyclization Studies. Cyclization of the dienediynol **9** was explored with a variety of acids, including trifluoroacetic acid, formic acid, and boron trifluoride, and in solvents such as trifluoroethanol, methylene chloride, acetonitrile, tetrahydrofuran, and pentane using VPC analysis with an internal standard to examine the product mixture. Satisfactory conversion of substrate **9** to tetracyclic compounds was observed by using trifluoroacetic acid in trifluoroethanol, but higher yields of tetracyclic ketones were obtained when the cyclization was conducted in a vigorously stirred biphasic mixture of formic acid and pentane (5:1) at 0 °C for 3–6 h.[15] Dilution experiments showed that the rate of the reaction diminished markedly when the ratio of pentane to formic acid was increased, suggesting that the cyclization was occurring at the interface of the emulsion. Methanolysis of the resulting enol formates produced an oil in 89% yield, which upon flash chromatographic purification yielded a crystalline solid containing a major and a minor tetracyclic ketone in 25–30% yield (56/44 mixture). The other products isolated from the crude cyclized material appeared to be primarily tricyclic hydrocarbons and polymeric material. No further attempts were made to identify the nontetracyclic components. Recrystallization (3×) of the solid yielded the major tetracyclic ketone **10** as colorless prisms, mp 137–141 °C.

Formation of Ring A of the Euphane Ring System. Reduction of ketone **10** with lithium aluminum hydride in ether gave an oily mixture of C-20 alcohols **24** (94/6 by VPC), which was converted in 99% overall yield to the crystalline acetate **25** (Scheme III). Acetate **25** was ozonolyzed with reductive workup and the resulting dione acetate **26** was converted directly to enone **27** by refluxing with sodium hydroxide in aqueous methanol (rigorously oxygen free) in 60% overall yield. (Phenylthio)-methylation[16] of **27** with benzenethiol and formaldehyde in the presence of triethanolamine gave **28** in 36% yield (Scheme III). Reduction of **28** with lithium in ammonia followed by trapping of the enolate with methyl iodide[17] gave C-4 dimethyl ketone **29** directly in 41% yield after chromatography. Oxidation of **29** with pyridinium chlorochromate[18] in methylene chloride containing sodium acetate afforded the desired dione **30** in quantitative yield as a crystalline solid, which was recrystallized to give colorless plates, mp 139–150 °C (with phase changes).

Synthesis of the Comparison Compound. Dione *l*-**30** was prepared from the natural product, euphol (**1a**) to prove that dione **30** possesses the euphane ring structure, including the trans-A/B ring stereochemistry. The degradation of the C-17 side chain of euphol (as the C-3 methyl ether) to the C-20 ketone was recently reported by Audouin and Levisalles.[21] A modification of this proce-

(14) Johnson, W. S.; Li, T.-t.; Harbert, C. A.; Bartlett, W. R.; Herrin, T. R.; Staskun, B.; Rich, D. H. *J. Am. Chem. Soc.* **1970**, *92*, 4461–4463.
(15) Bartlett, W. R.; Johnson, W. S. *Bioorg. Chem.* **1975**, *4*, 342–362.
(16) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091–1096.
(17) (a) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275–286. (b) Smith, A. B.; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685–3689.
(18) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.
(19) (a) Fried, J.; Edwards, J. A. *Organic Reactions in Steroid Chemistry*; Van Nostrand Reinhold: New York, 1972; Vol. 2, p 156. (b) Siddall, J.; Baddeley, G.; Edwards, J. *Chem. Ind. (London)* **1966**, 25.
(20) Fetizon, M.; Kakis, F. J.; Ragoussis-Ignatiadou, V. *Tetrahedron* **1974**, *30*, 3981–89. An authentic specimen of this material, mp 205–208 °C (reported mp 211–214 °C) was obtained by the previously described degradation of lanosterol (Ganem, B.; Kellogg, M. S. *J. Org. Chem.* **1974**, *39*, 575–77. Bernassan, J.-M.; Fetizon, M. *Synthesis* **1975**, 795–96). Oxidation of IV with pyridinium chlorochromate[18] in methylene chloride gave an authentic specimen of *d*-dione **31**.



(21) Audouin, M.; Levisalles, J. *Tetrahedron* **1983**, *39*, 2799.

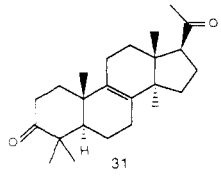
dure was employed in which the C-3 alcohol was protected during ozonolysis as the acetate.

Thus, euphol was obtained by extracting powdered *Euphorbia resinifera*.[22] The acetates of euphol and euphorbol (3:1 mixture after chromatography), prepared by standard methods, were subjected to ozonolysis, yielding the aldehyde **33** in 39% yield after chromatography (Scheme IV). Addition of excess phenyllithium, followed by ethanolysis of the C-3 acetate, provided the diol **34** in 77% yield. Oxidation with pyridinium chlorochromate gave dione **35**, which upon selective irradiation at 366 nm underwent Norrish type II photofragmentation at the phenyl ketone functionality, providing olefin **36** in 60% yield. Ozonolyis of olefin **36** yielded dione *l*-**30** in 80% yield, for comparison with dione **30**, obtained from cyclization.

The authentic comparison compound, dione *l*-**30**, was identical by chromatographic, 400-MHz ^{1}H NMR, solution IR, VPC coinjection, and mass spectral analyses with the corresponding dione **30** derived from cyclization. This correlation verifies the assignment of the trans ring A/B stereochemistry of dione **30** and provides proof that the stereochemistry at C-13, C-14, and C-17 in the predominant tetracyclic product of cyclization is indeed that found in the euphane ring system.

Studies of the Minor Tetracyclic Compounds from Cyclization. In an attempt to identify the minor tetracyclic compounds from the cyclization, a recrystallized sample of ketone **10** was submitted to epimerization conditions using refluxing methanolic potassium carbonate. Analysis employing VPC detected no production of the minor ketone from the cyclization. Similarly, mixture b containing two tetracyclic ketones was submitted to epimerization conditions using refluxing methanolic lithium methoxide and again no change in the composition of the mixture was detected. In a related experiment using potassium *tert*-butoxide in refluxing *tert*-butyl alcohol in the presence of oxygen, the tetracyclic ketone mixture b (38/62 ratio) was deacetylated to a mixture of new C(17) ketones, which was also formed in a 38/62 ratio.[19] Thus the tetracyclic ketones from cyclization of substrate **9** are not epimeric at C-17 but at C-13 and/or C-14.

The tetracyclic ketone mixture **a** (from chromatography of the crude product), containing ketone **10** and the two minor isomers (6:3:1 ratio), was submitted to the series of reactions described above (Scheme III) to give a mixture of diones **30a** (ketone **30** and its isomers) to establish that neither of the two minor ketones of cyclization mixture a were epimeric at both C-13 and C-14, i.e., lanostane derivatives. The known[20] dione **31**, obtained from lanosterol, was compared with the diones **30a**, derived from cyclization of substrate **9**, and was found to be different both spectrally and by VPC analysis, confirming that the minor tetracyclic ketones do not possess the lanostane nucleus.



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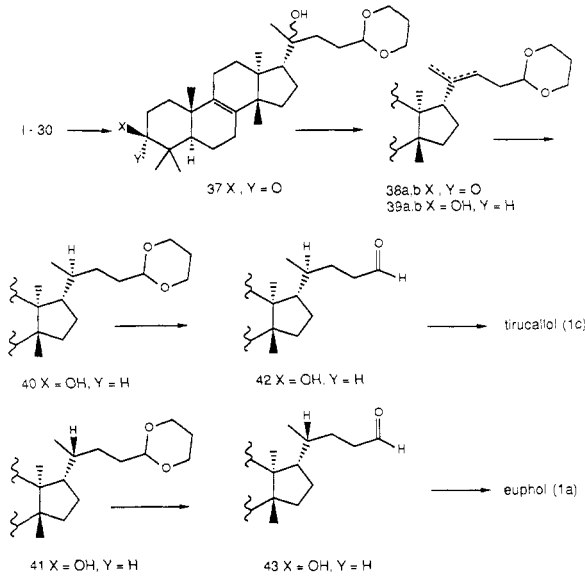
Synthesis of Tirucallol (1c) and Euphol (1a). Since the degradation of euphol to dione *l*-**30** was efficient, a relayed total synthesis of euphol (**1a**) and tirucallol (**1c**) became feasible. In theory, the most expedient method for constructing the C-17 side chains of euphol and tirucallol would be to directly deoxygenate the C(20) tertiary alcohol derived from selective addition of (4-methyl-3-pentenyl)magnesium bromide to dione *l*-**30**. All attempts to achieve clean deoxygenation, however, proved unsuccessful in this system. Likewise, our attempts to synthesize euphenol and tirucallenol (the C-20 epimer) by selective Wittig olefination of dione *l*-**30** with isohexyltriphenylphosphonium bromide followed by reduction of the C-20 olefin met with failure at the Wittig reaction.

Scheme V



The successful approach entailed selective addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane, prepared in tetrahydrofuran, to a toluene solution of dione *l*-**30** at 0 °C, providing compound **37** in 70% yield (Scheme V). When ether or tetrahydrofuran was used as solvent, only starting material *l*-**30** was recovered, presumably due to enolate formation competing with the addition.[23] Elimination of the tertiary alcohol in **37** was accomplished by adding methanesulfonyl chloride and triethylamine to a solution of **37** at 0 °C, providing **38a,b** in a 1:1 ratio after chromatography. Sodium borohydride reduction gave the alcohols **39a,b** in 88% yield. Hydrogenation with 5% Pt on carbon yielded alcohols **40** and **41** (2:1 ratio), which were separated by chromatography.[24]

The major isomer from hydrogenation, alcohol **40**, was hydrolyzed with 2.5% HCl in tetrahydrofuran to give aldehyde **42** in 58% yield. Reaction of **42** with the ylide derived from isopropyltriphenylphosphonium iodide and *n*-butyllithium in tetrahydrofuran at 0 °C in the presence of TDA-1[25] provided tirucallol (**1c**) in 74% yield.

The minor isomer from hydrogenation, alcohol **41**, was hydrolyzed as described above to give aldehyde **43** in 94% yield, which was converted in an analogous manner to euphol (**1a**) in 70% yield by Wittig olefination.

Comparison of authentic euphol by ^{1}H NMR, solution IR, melting point, mass spectral analysis, VPC, and optical rotation with the euphol derived by relay synthesis from dione *l*-**30** showed the authentic euphol to be identical with the synthetic euphol. Unfortunately, an authentic sample

(22) The powdered *Euphorbia resinifera* was obtained from Carl Roth Chemical Company (Germany) via Atomergic Chemetals Corp., Farmingdale, NY.

(23) Canonne, P.; Foscolos, G.; Caron, H.; Lemay, G. *Tetrahedron* **1982**, *38*, 3563.

(24) Hydrogenation of similar C-20,C-21 olefins have shown similar ratios of C-20 isomers; see: Dubois, G. E. *J. Org. Chem.* **1982**, *47*, 5035.

(25) Stafford, J. A.; McMurry, J. E. *Tetrahedron Lett.* **1988**, *29*, 2531.

of tirucallol could not be obtained; however, melting point and optical rotation are in accord with literature values.[2] The ^{1}H NMR, solution IR, and mass spectral analysis of tirucallol vary only slightly from the corresponding properties of euphol (i.e., chemical shift of C(21) methyl doublet in the NMR). These facts coupled with the method of synthesis insure that the major isomer was indeed tirucallol.

Discussion

In regard to the cyclization of the dienediyne **9**, the formation of a compound possessing the euphane configuration with the apparent total absence of compounds having the lanostane configuration could not have been anticipated at the outset of this study. Persuasive arguments can be made that ring strain inherent in the euphane ring system would render such compounds unstable under acid-catalyzed cyclization conditions. Indeed, the formation of lanostanes and absence of euphanes in the cyclization studies of van Tamelen and co-workers,[5] the unexpected stability of the cis A/B ring juncture in the butyrospermol intermediates reported by Kolaczkowski and Reusch,[3] and the known propensity of the euphanes to undergo facile acid-catalyzed backbone rearrangement to the isoeuphanes[2] all point to the acid lability of euphanes. The source of the euphane lability is thought to be the boat-like conformations of both the B and C rings caused by the 8,9-olefinic bond and the 13α and 14β methyl groups at the C/D ring juncture.[2]

During the biosynthesis of the euphanes and the lanostanes it has been proposed[2,5] that the cyclization substrate, squalene oxide, is restricted in its folded conformations by the enzymes.[26] In the nonenzymic cyclization of **9**, external template control over the process cannot be invoked to explain the observed selectivity of the cyclization. Whether the selective formation of the euphane configuration is due to preferential cyclization along reaction pathway $A_1 \rightarrow B_1$ (Scheme I) or is due to alternate reaction pathways from cation B_2 (e.g., formation of tricyclics or C/D cis-tetracyclics) is not known.

The relatively modest yield of tetracyclic ketone **10** (ca. 16%) is in keeping with the major tenet emerging from these cyclization studies:[1] for maximum efficiency of cyclization of a polyolefinic substrate, those points where cationic charges develop in the transition state must be in a stabilized form. Thus the high energy of the vinyl cations A_1/A_2 in ring B would be expected to produce an unfavorable effect upon the yield of tetracyclic products.

In conclusion, the efficiency of the synthesis of cyclization substrate **9** was enhanced by the development of a high-yield one-step conversion of the allylic *tert*-butyl ether **16** to the allylic chloride **18**. The conversion of ketone **10**, the major tetracyclic product of the acid-catalyzed cyclization of **9**, to dione **30**, possessing the 5α,10β,13α,14β,17α configuration found in the euphane class of triterpenoids, constitutes the first reported successful construction of this ring system. Elaboration of the C-17 side chain in dione *l*-**30**, derived by degradation of the natural product, gave euphol (**1a**) and tirucallol (**1c**), thus providing the first formal total synthesis of members of this class of plant triterpenes.

Experimental Section

General Considerations. The prefix *dl* has been omitted from the names of the racemic compounds described in this section. Melting points were determined on a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers. All reactions were run under an atmosphere of nitrogen or argon. Tetrahydrofuran and ethyl ether were distilled from sodium benzophenone ketyl. Hexamethylphosphoric acid triamide (HMPA) was distilled from sodium metal. Dichloromethane was distilled from calcium hydride. Anhydrous formic acid was distilled from boric anhydride–phthalic anhydride and stored at 0 °C. ^{1}H NMR spectra were recorded at 100, 300, or 400 MHz in deuteriochloroform. GC-MS were run using a 2 m × 2 mm 3% OV-17 glass column, or a 25-m SE-54 capillary column. Vapor-phase chromatographic (VPC) analyses were performed on $^1/_8$ in. glass columns (6 or 12 ft., 3% OV-17) or a 15-m SE-54 capillary column (hydrogen carrier gas) or a 50-m SE-54 capillary column (hydrogen carrier gas). Analytical and preparative thin layer chromatography (TLC) were performed on silica gel H or $60F_{254}$ plastic plates (E. Merck AG) at 0.25 mm or 1.0 mm thicknesses. Analytical plates were visualized by use of a UV light followed by an iodine chamber or sprays of anisaldehyde or phosphomolybdic acid. Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh) or Florisil. Evaporative distillation refers to bulb-to-bulb short-path distillation in which the bulb was heated in a hot-air oven. The cited temperatures for these distillations refer to the highest temperature reached during the distillation.

***trans*-1-*tert*-Butoxy-2,3-dimethyl-4-chloro-2-butene (12).** A published procedure[10] was modified. A cold (−78 °C) solution of 26.5 g (0.322 mol) of 2,3-dimethyl-1,3-butadiene (**11**) in dichloromethane (600 mL) was stirred under argon while freshly prepared[28] *tert*-butyl hypochlorite (35 g, 0.322 mol) was added over a period of 15 min. The mixture was allowed to warm to −10 °C and then was stirred at this temperature for 30 min. The mixture was then allowed to warm to 10 °C over a period of 60 min and then was cooled to −10 °C, poured into aqueous sodium bisulfite, and extracted with dichloromethane[27] to give 22 g of colorless oil. Note that the reaction times and temperatures are critical as an exothermic side reaction sets in easily, resulting in a lower yield of the desired product. The desired 1,4-adduct comprised 54% (50 m, 110 °C, t_R 5.97 min) of the mixture. Short-path distillation from barium oxide (bp 38–67 °C, 0.2 mm) followed by distillation through a spinning band column gave 8.8 g of a mixture (3:7) of the 1,2- and 1,4-adducts (bp 26–40 °C, 1 mm) and 9.7 g (15% yield) of the desired 1,4-adduct **12**[10] (bp 48–49 °C, 1 mm), which was 92% one peak on VPC (50 m, 150 °C, t_R 3.15 min); TLC (R_f 0.65, 19:1 hexane–ethyl acetate, basic alumina): IR (film) 9.5, 11.4 μm; ^{1}H NMR 1.21 (s, 9 H), 1.8 (s, 6 H), 3.87 (s, 2 H), 4.09 (s, 2 H).

***trans*-1-*tert*-Butoxy-2,3-dimethyl-2-octen-6-yne (16).** A sample of allene (6.5 mL, 0.105 mol) was condensed in a dry ice/acetone bath and was added via cannula to dry ether (100 mL) under an argon atmosphere at −78 °C. Then *n*-butyllithium (84 mL, 2.5 M, 0.210 mol) in hexane was added slowly by syringe while maintaining the temperature of the reaction below −50 °C.[13] The temperature was allowed to rise to −20 °C, during which a thick, white precipitate suddenly formed. The mixture was stirred at −20 °C for 15 min, then a solution of allylic chloride **12** (10 g, 0.0525 mol) in ether (50 mL) was added dropwise over a 15-min period. The mixture was allowed to warm to room temperature, stirred for 3 h, and then cooled to −25 °C. HMPA (70 mL) was added via syringe, affording a deep red solution, and then methyl iodide (13.9 mL, 32 g, 0.225 mol) was added, causing the formation of a white precipitate. The mixture was allowed to warm to room

(26) Or, alternatively, enzymatic point charge stabilization directs the cyclization process, as discussed in ref 1a.

(27) In cases where products were isolated by solvent extraction the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent, then the organic layers were combined and washed with saturated brine. The organic layer was dried over anhydrous sodium sulfate, magnesium sulfate, or potassium carbonate and filtered, and the solvent was evaporated under reduced pressure (water aspirator) on a rotary evaporator. The use of the term "wash" indicates washing the combined organic layers with saturated aqueous sodium bicarbonate solution ("base wash"), with dilute aqueous hydrochloric acid ("acid wash"), or with the indicated solution prior to the aforementioned washing with water.

(28) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 184.

(29) Johnson, W. S.; Schneider, W. P. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 132.

temperature, stirred for 1 h, and then was poured into ice water (300 mL) and extracted with ether.[27] The orange oil was taken up in pentane (200 mL) and washed with brine. A yellow oil was produced, which was distilled to afford the enyne ether **16** (8.7 g, 85% yield) as a colorless oil, bp 66 °C (0.25 mm), which was 91% one peak on VPC (50 m, 150 °C, t_R 4.62 min) and one spot on TLC (R_f 0.37, 5% ethyl acetate–hexane). The analytical specimen of **16** was obtained as a colorless oil by preparative VPC (4 ft, 5% SE-30 on Chromosorb G 45/50, 70 °C) followed by evaporative distillation at 100 °C (0.20 mm): IR (film) 6.85, 7.35, 8.3, 9.4, 9.8, 11.2 μm; ^{1}H NMR 1.22 (s, 9 H), 1.71 (s, 6 H), 1.77 (t, J = 2.4 Hz, 3 H), 2.1–2.3 (m, 4 H), 3.86 (s, 2 H).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.77; H, 11.54. Found: C, 81.02, H, 11.54.

***trans*-1-Chloro-2,3-dimethyl-2-octen-6-yne (18).** A cold (2 °C) solution of acetyl chloride (37 g, 0.50 mol) in carbon tetrachloride (250 mL) was mixed vigorously via mechanical stirrer as a solution of anhydrous ferric chloride (0.850 g, 5.25 mmol) in ether (25 mL) was added via syringe over a period of 5 min. A solution of the allylic ether **16** (8.0 g, 38.5 mmol) in carbon tetrachloride (5 mL) was added dropwise via syringe, keeping the temperature below 7 °C. The mixture was stirred at 6 °C for 1 h as the initial golden solution turned brown. Potassium carbonate (20 g) was added as the mixture was cooled to 0 °C. Excess acetyl chloride was destroyed by the cautious addition of methanol (40 mL) and the mixture was extracted with dichloromethane[27] to give an orange residue, which was distilled to afford allylic chloride **18** (6.6 g, 82% yield) as a colorless oil, bp 74 °C (0.1 mm), which was 83% one peak on VPC (50 m, 110 °C, t_R 7.72 min) and one spot on TLC (R_f 0.59, 5% ethyl acetate–hexane): IR (film) 6.94, 7.35, 8.1, 9.25, 11.4, 14.5 μm; ^{1}H NMR 1.75–1.79 (m, 9 H), 2.1–2.35 (m, 4 H), 4.10 (s, 2 H).

***trans*-5,6-Dimethyl-5-undecene-1,9-diyne (19).** A sample of allene (5.6 g, 8.6 mL, 0.140 mmol) was condensed in a dry ice/acetone bath and added via cannula to dry ether (100 mL) under an argon atmosphere at −78 °C. *n*-Butyllithium (2.5 M, 112 mL, 0.280 mol) solution in hexane was added slowly via syringe while maintaining the reaction temperature below −50 °C.[13] The solution was allowed to warm to −20 °C over a period of 30 min, during which a thick, white precipitate suddenly formed. The reaction was maintained at −20 °C for 15 min; then a solution of the allylic chloride **18** (11.0 g, 64.5 mmol) in dry ether (100 mL) was added dropwise over a 15-min period. The mixture was allowed to warm to room temperature and stirred for 2 h before being poured into ice water (200 mL). Ether extraction[27] gave a yellow oil, which was distilled to afford diyne **19** as a colorless oil (9.4 g, 84% yield). Chromatography on silica gel (pentane eluant) gave a colorless oil (6.8 g), bp 74 °C (0.5 mm), which was 96% one peak by VPC (50 m, 220 °C, t_R 2.59 min) and one spot on TLC (R_f 0.38, hexane): IR (film) 3.04, 6.94, 7.25, 9.1, 9.3, 15.9 μm; ^{1}H NMR 1.68 (s, 6 H), 1.77 (t, J = 2.4 Hz, 3 H), 1.92 (t, J = 2.4 Hz, 1 H), 2.1–2.3 (m, 8 H); MS m/z 173 (M^+ − H, 5), 159 (M^+ − CH_3, 45).

Anal. Calcd for $C_{13}H_{18}$: C, 89.55; H, 10.45. Found: C, 89.35; H, 10.47.

15,15:18,18-Bis(ethylenedioxy)-6,7-dimethyl-*trans*-nonadec-6-ene-2,10-diyne (21). A cold (−40 °C) solution of the acetylene **19** (4.83 g, 27.7 mmol, freshly evaporatively distilled) in tetrahydrofuran (550 mL) was stirred under an argon atmosphere while a solution of methyllithium (1.5 M, 18.5 mL, 27.7 mmol) in hexane was added. The solution was stirred at room temperature for 3 h, and then HMPA (55 mL) was added, causing the reaction mixture to turn burgundy red. The known[15] bis-ketal bromide **20** (8.5 g, 27.5 mmol, chromatographed and evaporatively distilled immediately before use) in tetrahydrofuran (20 mL) was added in one portion. The mixture was stirred at room temperature for 17 h and then poured into ice-cold brine (600 mL). After extraction (4:1 hexane–ether) and wash with saturated LiCl solution, most of the solvent was removed at reduced pressure and the residue was evaporatively distilled (190 °C, 1 mm) to give a forerun. Continued distillation (230 °C, 0.01 mm) afforded the acetylene **21** (9.34 g, 84% yield) as a yellow oil, which showed one spot on TLC (R_f 0.54, 1:1 hexane–ethyl acetate) and was 97% one peak on VPC (15 m, 250 °C, t_R 3.34 min). The analytical specimen of **21** was prepared by chromatography (Woelm basic alumina, activity grade III, 9:1 hexane–ethyl acetate) followed by evaporative distillation at 200 °C (0.005 mm): IR (film) 6.9, 7.28, 7.8, 8.0, 8.2, 8.8, 9.2, 9.4, 9.6, 10.5, 11.0, 11.6 μm; ^{1}H NMR 1.32 (s, 3 H), 1.67 (br s, 6 H), 1.79 (t, J = 2.4 Hz, 3 H), 1.4–1.75 (m, 10 H), 2.1–2.3 (m, 8 H), 3.96 (s, 8 H); MS m/z 387 (M^+ − CH_3, 2), 188 (M^+ − $C_{16}H_{22}$, 100).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.39; H, 9.47.

13,14-Dimethyl-*trans*-nonadec-13-ene-9,17-diyne-2,5-dione (22). Pyridinium tosylate (7.0 g) was added to a solution of bis-ketal **21** (9.8 g, 24.4 mmol) in acetone (500 mL) and water (70 mL) and the mixture was stirred under argon at reflux for 39 h. Saturated sodium bicarbonate was added (150 mL) and the solvent was removed at reduced pressure. Extraction with ether[27] gave dione **22** (7.7 g, 100% yield) as a yellow oil, which showed one spot on TLC (R_f 0.44, 1:1 pentane–ether) and one peak on VPC (15 m, 250 °C, t_R 1.08 min): IR (film) 5.85, 7.3, 8.5, 9.1 μm; ^{1}H NMR 1.67 (s, 6 H), 1.73 (t, J = 2.4 Hz, 3 H), 2.1–2.3 (m, 10 H), 2.19 (s, 3 H), 2.57 (t, J = 6.0 Hz, 2 H), 2.69 (m, 4 H); MS m/z 299 (M^+ − CH_3, 10), 43 (C_2H_3O, 100).

3-Methyl-2-(7,8-dimethyl-*trans*-tridec-7-ene-3,11-diynyl)-2-cyclopentenone (23). A solution of dione **22** (7.7 g, 25 mmol) in water (300 mL) and methanol (300 mL) containing sodium hydroxide (6.2 g) was deoxygenated thoroughly and stirred for 10 h at 70 °C under an atmosphere of argon. The resulting golden solution was allowed to cool to room temperature, and saturated ammonium chloride solution (100 mL) was added. The solvent was removed at reduced pressure and the residue was extracted[27] with ether to give an orange oil. Evaporative distillation at 215 °C (0.15 mm) afforded enone **23** (6.95 g, 96% yield) as a yellow oil, which showed one spot on TLC (R_f 0.36, 1:1 hexane–ethyl acetate) and one peak on VPC (15 m, 220 °C, t_R 3.07 min). An analytical specimen of **23** was obtained as a colorless oil by preparative TLC (4:1 hexane–ether) followed by evaporative distillation (200 °C, 0.5 mm): IR (film) 5.90, 6.06, 6.96, 7.25, 8.5, 9.3, 9.5 μm; ^{1}H NMR 1.66 (s, 6 H), 1.77 (t, J = 2.4 Hz, 3 H), 2.10 (s, 3 H), 2.1–2.6 (m, 16 H); MS m/z 281 (M^+ − CH_3, 11), 41 (C_2OH, 100).

Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.81; H, 9.54.

1,3-Dimethyl-2-(7,8-dimethyl-*trans*-7-tridecene-3,11-diynyl)-2-cyclopenten-1-ol (9). A solution of methyllithium/lithium bromide (1.5 M, 26.8 mL, 40 mmol) in ether was added over 5 min to a cold (−78 °C) solution of enone **23** (2.5 g, 8.48 mmol) in dry ether (750 mL) under an atmosphere of argon. The mixture was stirred at −78 °C for 2 h and then treated with dry 2-propanol (2.15 g, 43 mmol) and stirred for 30 min. The resulting mixture was treated again with methyllithium solution (14 mL, 20 mmol), stirred for 30 min, and treated as before with 2-propanol (1.32 g, 22 mmol). The reaction was allowed to warm to room temperature and then was treated with methyllithium solution again (5.0 mL, 7.5 mmol) and stirred for 30 min before being poured into brine (100 mL) and extracted with ether[27] to give alcohol **9** (2.8 g, 99% yield) as a pale yellow oil, which showed one spot on TLC (R_f 0.56, 1:1 pentane–ether) and two peaks on VPC resulting from dehydration of the tertiary allylic alcohol to give two regioisomeric trienediynes in a ratio of 7:3 (15 m, 220 °C, t_R 1.77, 1.95 min): IR (film) 2.9, 6.9, 7.2, 9.1, 11.5, 13.5 μm; ^{1}H NMR 1.28 (s, 3 H), 1.62 (s, 9 H), 1.77 (m, 3 H), 2.1–2.5 (m, 17 H).

Cyclization of Dienediynol 9 with Formic Acid in Pentane To Give Tetracyclic Mixture b. Isolation of 3,14-Dimethyl-4-*A*-nor-13α,14β,17α-pregna-3,8-dien-20-one (10). A cold (5 °C) mixture of allylic alcohol **9** (2.8 g, 8.5 mmol) in pentane (1500 mL) was stirred vigorously by mechanical stirrer under an argon atmosphere as formic acid (500 mL) was added. The progress of the reaction was followed by VPC analysis of aliquots. After stirring for 9 h at 5 °C, the pentane layer was decanted into a flask containing potassium carbonate (25 g) and was stirred for 30 min. The formic acid layer was extracted with pentane (2 × 100 mL) and the combined pentane layers were washed with aqueous sodium bicarbonate solution and brine. Removal of solvent at reduced pressure left an orange oil, which was dissolved in methanol (350 mL) containing 3.5 g of potassium carbonate. The mixture was stirred for 1 h under argon at 65 °C and then poured into brine (100 mL) overlaid with ether (200 mL) and extracted with ether[27] to give an orange gum (2.4 g, 100% yield)

that showed four spots on TLC (3:1 pentane–ether) and numerous peaks on VPC (15 m, 220 °C, 2.16 min, 21%; 2.21 min, 14%). The crude mixture was purified by flash chromatography on silica gel (10% ether–pentane) to afford 443 mg (20% yield) of a crystalline solid (mixture **b**) which showed one spot on TLC (R_f 0.45, 3:1 pentane–ether) and two peaks on VPC (15 m, 220 °C, t_R 2.15 min, 56%; 2.21 min, 44%). Another fraction consisted of 141 mg (6% yield) of a gum, which also showed two major peaks on VPC (2.15 min, 44%, 2.21 min 27%). The first fraction was further purified by recrystallization from methanol (three times) to give ketone **10** as colorless prisms (phase changes 135–140 °C, mp 140–141 °C), which showed one peak on VPC (50 m, 220 °C, 9.39 min): IR (CCl_4) 5.97, 6.9, 7.25, 7.4, 8.3, 8.5 μm; ^{1}H NMR 0.65 (s, 3 H), 0.99 (s, 6 H), 1.61 (s, 3 H), 2.12 (s, 3 H), 2.89 (t, J = 6 Hz, 1 H).

Anal. Calcd for $C_{22}H_{32}O$: C, 84.54; H, 10.34. Found: C, 84.81; H, 10.19.

Cyclization of Dienediynol 9 with Trifluoroacetic Acid in Trifluoroethanol. Preparation of Tetracyclic Mixture a. A cold (0 °C) solution of trifluoroacetic acid (5.0 mL, 3.3 g, 0.029 mol) and 100 mL of trifluoroethanol was stirred under argon while a solution of allylic alcohol **9** (1 g, 3.2 mmol) in 40 mL of trifluoroethanol was added over a period of 1.5 h. The resulting mixture, which eventually turned deep red, was stirred at 0 °C for 2 h, and then was cooled to −45 °C. Anhydrous potassium carbonate (25 g) was added in one portion, the suspension was stirred vigorously for 45 min, and then 3 g of potassium hydroxide in 15 mL of trifluoroethanol was added. The volatile material was removed at reduced pressure and the residue was extracted with ether[27] to give a yellow oil which was filtered through Florisil (15% ethyl acetate–hexane) and evaporatively distilled (150 °C, 0.01 mm) to give 0.94 g (92% yield) of a pale yellow oil. Chromatography on silica gel (5% ethyl acetate–hexane) afforded 0.43 g (44% yield) of **10a** as a colorless oil, which showed one spot on TLC (R_f 0.25, 5% ethyl acetate–hexane) and three peaks in the ratio 6:3:1 on VPC (90% of the total peak area).

Reduction of Ketone 10 and Ketone Mixture a. A. Isolation of 3,14-Dimethyl-4-*A*-nor-13α,14β,17α-pregna-3,8-dien-20-ol (24). A solution of ketone **10** (120 mg, 0.39 mmol) was stirred under argon at −78 °C while lithium aluminum hydride (1.0 M in tetrahydrofuran, 2.0 mL, 2.0 mmol) was added dropwise over a period of 5 min. The mixture was stirred at room temperature for 30 min and quenched by the dropwise addition of water (100 mg) followed by 15% potassium hydroxide (100 mg) solution and then water (300 mg). The white suspension was stirred for 15 min, then anhydrous magnesium sulfate was added, and the mixture was stirred, filtered (ether wash), and concentrated by rotary evaporation to afford alcohol **24** (121 mg, 100% yield) as a colorless gum, which showed one spot on TLC (R_f 0.22, 3:1 pentane–ether) and two peaks on VPC (50 m, 225 °C, t_R 8.22 min, 93%; 8.60 min, 5%).

The analytical specimen was obtained as a colorless oil by evaporative distillation: IR (film) 2.98, 6.9, 7.3, 8.8, 9.2, 9.7, 10.2, 11.2 μm; ^{1}H NMR 0.82 (s, 3 H), 0.94 (s, 3 H), 0.98 (s, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.62 (s, 3 H), 1.1–2.6 (m, 17 H), 4.87 (m, 1 H); MS m/z 314 (M^+, 4), 299 ($M^+ - CH_3$, 100).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 84.15; H, 11.04.

B. Preparation of Tetracyclic Alcohols 24a. In a similar manner, cyclization mixture a (150 mg, 0.48 mmol) was reduced with lithium aluminum hydride to afford a colorless oil (145 mg, 95% yield). Mixture **24a** showed one spot on TLC (R_f 0.53, 1:1:3 methylene chloride–acetone–hexane) and two major peaks on VPC (5% OV-17, 215 °C, t_R 45 min and 48 min, ratio 3:2): IR (film) 2.94, 6.9, 7.3 μm; ^{1}H NMR 0.74 (br s, 2.5 H), 0.83 (s, 0.5 H), 0.95 (s, 2.5 H), 1.0 (s, 3 H), 1.12 (d, J = 9 Hz, 3 H), 1.60 (s, 3 H).

3,14-Dimethyl-4-*A*-nor-13α,14β,17α-pregna-3,8-dien-20-ol Acetate (25). A solution of alcohol **24** (121 mg, 0.39 mmol) in pyridine (1.6 g, 20 mmol) and acetic anhydride (1.0 g, 10 mmol) of was stirred for 17 h at room temperature under an argon atmosphere. The solution was then cooled to 0 °C, lactic acid (0.9 g, 10 mmol) was added, and the solution was stirred for 15 min. Ether extraction[27] followed by filtration through Florisil (2:1 pentane–ether) gave acetate **25** (137 mg, 100% yield) as a white crystalline solid, mp 127–129 °C, which showed one spot on TLC (R_f 0.42, 10% ethyl acetate–hexane) and two peaks, ratio 92:5, on VPC (50 m, 225 °C): IR (CCl_4) 5.79, 6.9, 7.3, 8.05 μm; ^{1}H NMR 0.69 (s, 3 H), 0.95 (s, 3 H), 0.97 (s, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.61 (s, 3 H), 2.03 (s, 3 H), 2.1–2.5 (m, 17 H), 4.87 (m, 1 H).

Ozonolysis and Cyclodehydration of Acetate 25 and Alcohol Mixture 24a. A. Preparation of 14-Methyl-3-oxo-13α,14β,17α-pregna-4,8-dien-20-ol (27). Ozone was bubbled through a cold (−78 °C) solution of 137 mg (0.38 mmol) of acetate **25** in 50 mL of methylene chloride and 10 mL of anhydrous methanol containing 0.8 mL of pyridine until a permanent blue color appeared. Excess ozone was immediately removed by bubbling nitrogen through the mixture. Acetic acid (5 mL) and zinc dust (1 g, 15 mmol) were added, the suspension was warmed slowly to 0 °C with vigorous stirring, and after 30 min the mixture was allowed to warm to room teperature and stirred for 16 h. The reaction product was then extracted with ether[27] to give a colorless oil, which was purified by flash chromatography on silica gel (ether) to afford 139 mg (94% yield) of dione **26** as a colorless oil, which showed one spot on TLC (R_f 0.65, 1:1:3 methylene chloride–acetone–hexane) and three peaks on VPC, ratio 83:5:7 (15 m, 220 °C): IR (film) 5.82, 5.88, 6.9, 7.3, 8.1, 8.6, 9.3, 9.5, 9.8 μm; ^{1}H NMR 0.76 (s, 3 H), 1.01 (s, 3 H), 1.17 (s, 3 H), 1.19 (d, J = 6 Hz, 3 H), 2.03 (s, 3 H), 2.09 (s, 3 H), 4.88 (m, 1 H).

A solution of dione **26** (138 mg, 0.34 mmol) in 20 mL of methanol was degassed thoroughly with O_2 scrubbed argon (chromous chloride solution[30]). Then a solution of sodium hydroxide (0.5 g, 8.3 mmol) in freshly distilled water (10 mL) was thoroughly deoxygenated and added to the dione solution. The resulting yellow solution was stirred in the dark, under an oxygen-free argon atmosphere at 70 °C for 9 h. The solution was cooled to room temperature, treated with saturated ammonium chloride solution (40 mL), and extracted with ether,[27] giving a yellow foam. Flash chromatography on Florisil (4:1 pentane–ether) afforded enone **27** (71 mg, 63% yield) as a pale yellow foam, which showed one spot on TLC (R_f 0.42, 1:1 ethyl acetate–hexane) and three peaks on VPC, ratio 89:7:4 (50 m, 250 °C): IR ($CDCl_3$) 2.94, 6.02, 6.18, 6.9, 7.3, 8.1 μm; ^{1}H NMR 0.83 (s, 3 H), 0.98 (s, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.32 (s, 3 H), 3.78 (m, 1 H), 5.78 (s, 1 H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.65; H, 9.66.

B. Preparation of Enone Mixture 27a. In a similar manner, the aforementioned alcohol mixture **24a** (125 mg, 0.40 mmol) was ozonolyzed to afford 128 mg (93% yield) of the dione mixture as a colorless oil, which showed one spot on TLC (R_f 0.38, 1:1:3 methylene chloride–acetone–hexane) and one peak on VPC (5 ft, 3% OV-17, 250 °C): IR (film) 2.94, 5.85, 7.35, 11.2 μm; ^{1}H NMR 0.9 (s, 3 H), 1.0 (s, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.15 (s, 3 H), 2.05 (s, 3 H).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: 76.30; H, 10.10.

In a similar manner, a solution of 90 mg (0.26 mmol) of the aforementioned dione mixture was cyclodehydrated to afford 77 mg (91% yield) of enone mixture **27a** as a pale yellow oil, which showed one spot on TLC and one peak on VPC (18 ft, 5% OV-17, 280 °C): IR (film) 2.94, 5.85, 6.02, 6.85, 7.25, 10.9 μm; ^{1}H NMR 0.83 (s, 2.5 H), 0.87 (s, 0.5 H), 0.92 (s, 0.5 H), 0.97 (s, 2.5 H), 1.15 (d, J = 8 Hz, 3 H), 1.30 (s, 1.2 H), 1.33 (s, 1.8 H), 5.72 (s, 1 H).

4-(Phenylthio)methylation of Enone 27 and of Enone Mixture 27a. A. Preparation of 28. A published procedure[16] was used. A solution of the enone **27** (70 mg, 0.21 mmol), triethanolamine (2 g), benzenethiol (150 mg, 1.4 mmol), and 37% aqueous formaldehyde solution (0.4 mL, 5 mmol) was heated at 120 °C under argon (oxygen scrubbed) for 25 h in the dark. The mixture was cooled to room temperature and then extracted with methylene chloride[27] to give a yellow oil. Chromatography on Florisil (1:1 ether–pentane) afforded enone **28** (32 mg, 36% yield) as a pale yellow foam, which showed one spot on TLC (R_f 0.46, 1:1 ethyl acetate–hexane): IR (film) 2.92, 3.28, 6.06, 6.9, 7.3, 7.5, 9.2 μm; ^{1}H NMR 0.82 (s, 3 H), 0.97 (s, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.29 (s, 3 H), 3.90 (dd, 2 H), 3.75 (m, 1 H), 7.25 (m, 5 H).

Anal. Calcd for $C_{29}H_{38}O_2S$: C, 77.30; H, 8.50. Found C, 77.33; H, 8.49.

B. Preparation of Mixture 28a. In a similar manner, a solution of the aforementioned enone mixture **27a** (50 mg, 0.14

(30) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York; Vol. 1, p 149.

mmol) was (phenylthio)methylated to afford 49 mg (78% yield) of enone mixture **28a** as a yellow oil, which showed one spot on TLC (R_f 0.40, 1:1:3 methylene chloride–acetone–hexane): ^{1}H NMR 0.81 (s, 2.5 H), 0.84 (s, 0.5 H), 0.97 (s, 2.5 H), 1.16 (d, J = 8 Hz, 3 H), 1.27 (s, 3 H), 3.89 (s, 2 H), 3.7 (m, 1 H), 7.25 (m, 5 H).

Reductive Methylation of Enone 28 and Enone Mixture 28a. A. Preparation of 4,4,14-Trimethyl-3-oxo-13α,14β,17α-pregn-8-en-20-ol (29). Published procedures[17] were modified. A solution of enone **28** (31 mg, 0.0742 mmol) in tetrahydrofuran (2 mL) was added dropwise to a solution of lithium wire (25 mg, 3.6 mmol) in liquid ammonia (10 mL) at −33 °C. The blue mixture was stirred for 15 min at −33 °C and then isoprene (5 drops) was added until the mixture became white, followed by tetrahydrofuran (3 mL) and iodomethane (0.32 mL, 0.72 g, 5 mmol), and the pale yellow solution was stirred at −33 °C for 30 min. The reaction was quenched with saturated ammonium chloride (5 mL) and extracted with ether[27] to give an oil. Chromatography on Florisil (3:2 pentane–ether) afforded ketone **29** (11 mg, 41% yield) as a nearly colorless oil, which showed one spot on TLC (R_f 0.25, 1:1 ether–hexane) and four peaks (ratio 7:6:9:71) on VPC (50 m, 290 °C): IR (film) 2.9, 5.9, 6.9, 7.3, 9.0, 9.3, 10.0 μm; ^{1}H NMR 0.85 (s, 3 H), 0.93 (s, 3 H), 1.06 (s, 6 H), 1.10 (s, 3 H), 1.17 (d, J = 6 Hz, 3 H), 2.5 (m, 2 H), 3.78 (m, 1 H); MS m/z 358 (M^+, 12), 299 ($M^+ - C_3H_7O$, 100).

B. Preparation of Ketone Mixture 29a by a Two-Step Procedure. W-2 Raney nickel sludge (0.5 mL) in acetone was heated at reflux for 45 min, then a solution of enone mixture **28a** (30 mg, 0.065 mmol) in acetone (1 mL) was added, and the mixture was stirred for 2 h. After being cooled to room temperature, the mixture was filtered through Florisil (ethyl acetate), the solvent was distilled, and the product was evaporatively distilled (200 °C, 0.002 mm) to afford the 4-methyl enone mixture (21 mg, 93% yield) as a colorless oil, which showed one spot on TLC (R_f 0.36, 1:1:3 dichloromethane–acetone–hexane) and one peak on VPC (5 ft, 3% OV-17, 240 °C): ^{1}H NMR 0.83 (s, 2.5 H), 0.88 (s, 0.5 H), 0.93 (s, 0.5 H), 1.00 (s, 2.5 H), 1.16 (d, J = 9 Hz, 3 H), 1.28 (s, 3 H), 1.78 (s, 3 H), 3.72 (m, 1 H).

A cold (0 °C) solution of the 4-methyl enone mixture described above (31 mg, 0.092 mmol) in tetrahydrofuran (10 mL) was stirred while a solution of *sec*-butyllithium (1 M, 0.009 mL, 0.009 mmol) in hexane was added. The resulting solution was added dropwise via cannula to a stirred, cold (−33 °C) mixture of lithium wire (2.9 mg, 4.3 mg-atom) in liquid ammonia (10 mL, distilled from sodium). The blue mixture was stirred at −33 °C for 15 min, and then isoprene was added until the mixture became white. Iodomethane (2 g, 14 mmol) was added dropwise and the mixture was stirred at −33 °C for 20 min. The solvent was allowed to evaporate at room temperature and the residue was extracted with ether[27] to give a colorless oil. Chromatography on Florisil (17:3 hexane–ethyl acetate) afforded ketone mixture **29a** (30 mg, 95% yield) as a colorless oil, which showed one spot on TLC (R_f 0.35, 1:1:3 dichloromethane–acetone–hexane) and one peak on VPC (6 ft, 3% OV-1, 225 °C): IR (film) 2.94, 5.81, 6.83, 7.33, 8.0 μm; ^{1}H NMR 0.83 (s, 3 H), 0.92 (s, 3 H), 1.00 (d, J = 9 Hz, 3 H), 1.10 (s, 3 H), 1.15 (s, 3 H), 1.20 (s, 3 H).

Oxidation of Alcohol 29 and Alcohol Mixture 29a. A. Preparation of 4,4,14-Trimethyl-13α,14β,17α-pregn-8-ene-3,20-dione (30). A published procedure was used.[18] A solution of alcohol **29** (10 mg, 0.028 mmol) in dichloromethane (3 mL) was added to a mixture of pyridinium chlorochromate (45 mg, 0.2 mmol), sodium acetate (20 mg, 0.2 mmol), and anhydrous magnesium sulfate (50 mg) in dichloromethane (2 mL). The mixture was stirred at room temperature for 2 h under argon and then was filtered through Florisil (ether) to afford dione **30** (10 mg, 100% yield) as a crystalline white solid, which showed one spot on TLC (R_f 0.50, 1:1 ether–hexane) and two major peaks on VPC (50 m, 250 °C, ratio 10:72). Low-temperature recrystallization from dry ether (−50 °C), followed by two recrystallizations from 1:1 ether–pentane (−20 °C), afforded dione **30** (2.5 mg) as colorless plates, mp 146–150 °C (with phase transition from plates to needles, 139–146 °C): IR (CCl_4) 2965, 1705, 1457, 1387, 1362, 1208, 1182, 1147, 1110 cm^{-1}; ^{1}H NMR 0.68 (s, 3 H), 0.98 (s, 3 H), 1.06 (s, 3 H), 1.07 (s, 3 H), 1.10 (s, 3 H), 2.13 (s, 3 H), 2.89 (t, J = 9 Hz, 1 H); MS m/z 356 (M^+, 33), 43 ($C_2H_3O^+$, 100).

B. Preparation of Dione Isomer Mixture 30a. In a similar manner, alcohol mixture **29a** (10 mg, 0.028 mmol) was oxidized to afford dione mixture **30a** as an amorphous white solid. VPC analysis of the mixture (12 ft, 3% OV-17, 235 °C) showed three peaks at 39, 41, and 42 min. GC-MS (3% OV-17, 250 °C) showed three peaks in a ratio of 6:3:1 with m/z of 356 (M^+, t_R 18 min) for the predominant substance: IR (CCl_4) 1705, 1460, 1350, 1250, 1110, 1000 cm^{-1}; ^{1}H NMR 0.68 (s, 1.2 H), 0.70 (s, 1.8 H), 0.97 (s, 3 H), 1.06 (s, 3 H), 1.10 (br s, 6 H).

***d*-4,4,14-Trimethyl-5α,14α-pregn-8-ene-3,20-dione (31).** A published procedure[18] was used. A solution of the known[20] alcohol (10β,13β,14α,17β), mp 249–251 °C (reported mp 254–256 °C), in dichloromethane (2 mL) was added via syringe to a mixture of pyridinium chlorochromate (17 mg, 0.078 mmol) and sodium acetate (6.0 mg, 0.064 mmol) in dichloromethane (4 mL). The mixture was stirred at room temperature for 2 h under argon and then filtered through Florisil (ether) to afford dione *d*-**31** (17 mg, 86% yield) as colorless prisms, mp 205–208 °C (lit.[20] mp 211–214 °C), which showed one spot on TLC (R_f 0.75, 4:7 hexane–acetone, 4 elutions) and one peak on VPC (under same conditions as VPC of mixture **30a**, 12 ft, 3% OV-17, 235 °C, t_R 45 min). The ^{1}H NMR and solution IR spectra were identical with the spectral data reported[20] for dione *d*-**31**: IR (CCl_4); ^{1}H NMR 0.63 (s, 3 H), 0.95 (s, 3 H), 1.04 (s, 3 H), 1.10 (br s, 6 H), 2.07 (s, 3 H).

Epimerization Experiments. A. With Methanolic Potassium Carbonate. A solution of ketone **10** (1.0 mg, one peak on VPC) in methanol (2 mL) containing potassium carbonate (0.3 g) was stirred under a nitrogen atmosphere at reflux for 35 min. Extraction with ether[27] gave a film, which showed one peak on VPC (15 m, 220 °C) identical in retention time (2.15 min) with the starting compound. The isomeric ketone found in the cyclization mixture has a retention time of 2.24 min under these VPC conditions.

B. With Methanolic Lithium Methoxide. A solution of the ketone mixture b (46 mg) from cyclization, showing two peaks on VPC (ratio 1:1.7, t_R 2.15, 2.24 min) in methanol (5 mL), was stirred under nitrogen as a solution of methanol (2 mL) containing methyllithium solution (1.0 mL, 1.5 M in hexane) was added dropwise. The solution was stirred at reflux for 24 h and extracted with ether[27] to give a colorless oil (40 mg), which showed two peaks on VPC identical with those found in the starting mixture.

C. With Potassium *tert*-Butoxide. A solution of potassium *tert*-butoxide was prepared from potassium metal and *tert*-butyl alcohol (3 mL) by a published procedure.[29] The solution was stirred under argon (not oxygen scrubbed) as a solution of ketone mixture b (2 mg, two peaks by VPC, 15 m, 220 °C, 2.15 min, 2.24 min, 1:1.7 ratio) in dry *tert*-butyl alcohol (1 mL) was injected by syringe. The solution was stirred at room temperature for 48 h and then extracted with ether[27] to give an oil, which showed two new peaks on VPC (15 m, 220 °C, 1.35 min, 1.39 min, ratio 1:1.7): ^{1}H NMR 0.85 (s, 3 H), 0.89 (s, 1.2 H), 0.90 (s, 1.8 H), 0.91 (s, 1.2 H), 0.93 (s, 1.8 H), 1.56 (s, 3 H); MS m/z 284 (M^+, 2), 269 ($M^+ - CH_3$, 100).

Isolation of *d*-Euphol (1a) and Euphorbol. Preparation of Euphyl Acetate (32), Mixed with Euphorbyl Acetate. Powdered *Euphorbium resinifera*[22] in acetone (90 mL) was heated at reflux for 30 h. After cooling to room temperature, the solids were filtered through Celite and washed with acetone. The filtrate was evaporated, giving a brown gum, which was chromatographed on flash silica gel (20 × 6 cm pad) using water aspirator vacuum (eluted with 100-mL portions of hexane–ethyl acetate, 3:1). The colorless solid obtained after evaporation of solvent was dissolved in pyridine (14 mL), acetic anhydride (4 mL) and 4-(dimethylamino)pyridine (0.1 g) were added, and the solution was stirred for 16 h at room temperature. Water was added and after 30 min the solution was extracted[27] with ether to give a colorless foam (3.13 g) as a 3:1 mixture of euphyl acetate (**32**) and euphorbyl acetate: ^{1}H NMR 5.07 (t, 1 H, J = 6 Hz), 4.78 (dd, 1 H, J = 11.7 Hz, J = 4.6 Hz), 2.03 (s, 3 H), 2.10–1.80 (m, 6 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 0.95 (s, 3 H), 0.86 (s, 3 H), 0.85 (s, 6 H), 0.83 (d, 3 H, J = 6.2 Hz), 0.72 (s, 3 H).

3β-Acetoxy-5α,13α,14β,17α-lanost-8-en-24-al (33). A 3:1 mixture of euphyl acetate (**32**) and euphorbyl acetate (2.69 g, 5.74 mmol) in dichloromethane (125 mL) containing pyridine (0.75 mL) was cooled to −78 °C and ozone was bubbled through the solution until starting material could not be detected by TLC analysis. Triphenylphosphine (0.75 g, 2.87 mmol) was added and the reaction mixture was warmed to room temperature. The

solution was extracted[27] to give a yellow foam. Chromatography on silica gel (5:1 hexane–ether) gave aldehyde **33** (0.99 g, 39% yield) as a colorless solid: ^{1}H NMR 9.74 (t, 1 H, J = 1 Hz), 4.48 (dd, 1 H, J = 11.7 Hz, J = 4.4 Hz), 2.50–2.28 (m, 2 H), 2.03 (s, 3 H), 0.95 (s, 3 H), 0.86 (s, 6 H), 0.85 (s, 3 H), 0.82 (d, 3 H, J = 5.8 Hz), 0.75 (s, 3 H); IR ($CDCl_3$) 5.83, 6.82, 7.27, 8.00, 9.17 μm.

3β-Hydroxy-24-phenyltrisnor-(25,26,27)-5α,13α,14β,17α-lanost-8-en-24-ol (34). Phenyllithium (2.0 M, 1.25 mL) was added to a solution of aldehyde **33** (0.50 g, 1.13 mmol) in tetrahydrofuran (60 mL) at −78 °C and then the reaction mixture was warmed to room temperature over 2 h. Saturated ammonium chloride was added and the product was extracted with ether,[27] giving a colorless oil, which was dissolved in 95% ethanol (50 mL). Potassium hydroxide (5%, 4 mL) was added and the solution was heated at reflux for 2 h. After cooling, solvent was removed under reduced pressure, saturated ammonium chloride was added, and the residue was extracted with ether[27] to give a colorless solid. Chromatography on silica gel (3:1 hexane–ethyl acetate) gave diol **34** (0.415 g, 77% yield) as colorless crystals, mp 177–180 °C: ^{1}H NMR 7.33 (m, 5 H), 4.61 (m, 1 H), 3.22 (dd, 1 H, J = 11.8 Hz, J = 4.6 Hz), 0.97 (s, 3 H), 0.93 (s, 3 H), 0.83 (d, 3 H, J = 6.8 Hz), 0.82 (s, 3 H), 0.78 (s, 3 H), 0.68 (s, 3 H); EIMS m/z calcd 478.3810, found 478.3819.

Anal. Calcd for $C_{33}H_{50}O_2$: C, 82.80; H, 10.52. Found: C, 81.98; H, 10.60.

***d*-3,24-Dioxo-24-phenyltrisnor-(25,26,27)-5α,13α,14β,17α-lanost-8-ene (35).** Pyridinium chlorochromate (0.375 g, 1.74 mmol) was added to a solution of diol **34** (0.380 g, 0.79 mmol) in dichloromethane (40 mL). After being stirred for 16 h at room temperature, the reaction mixture was filtered through silica gel (1:1 hexane–ethyl acetate), and solvent was evaporated to give 0.375 g (100% yield) of a colorless oil: VPC (15 m, 280 °C, 7.16 min, 100%); IR (film) 3.26, 3.36, 5.85, 5.92, 6.90, 7.24, 7.84, 8.26, 8.93, 9.80 μm; ^{1}H NMR 7.95 (d, 2 H, J = 7.3 Hz), 7.54 (t, 1 H, J = 7.5 Hz), 7.45 (t, 2 H, J = 7.5 Hz), 2.94 (m, 2 H), 2.52 (ddd, 1 H, J = 15.8 Hz, J = 10.0 Hz, J = 7.5 Hz), 2.44 (dq, 1 H, J = 15.8 Hz, J = 4.0 Hz), 1.07 (s, 3 H), 1.03 (s, 3 H), 0.89 (d, 3 H, J = 7.9 Hz), 0.88 (s, 3 H), 0.75 (s, 3 H); $[\alpha]^{22}_D$ = +62.1° (c = 0.11 in CH_2Cl_2).

Anal. Calcd for $C_{33}H_{46}O_2$: C, 83.50; H, 9.76. Found: C, 83.62; H, 9.86.

***d*-4,4,14-Trimethyl-20-methylene-5α,13α,14β,17α-pregn-8-en-3-one (36).** A solution of phenyl ketone **35** (0.375 g, 0.79 mmol) in benzene (300 mL) was purged with argon for 15 min and then irradiated at 366 nm (uranyl glass, Hanovia 400-W medium pressure mercury arc lamp) for 4.25 h. The solvent was evaporated and the residue chromatographed on silica gel (9:1 hexane–ether) to give compound **36** (0.170 g, 61% yield) as a colorless solid, VPC (15 m, 250 °C, 1.66 min, 100%), mp 151–153 °C: IR (evaporated film) 3.40, 5.88, 6.06, 6.83, 7.22, 8.13, 11.11 μm; ^{1}H NMR 4.84 (s, 1 H), 4.73 (s, 1 H), 2.50 (m, 2 H), 1.75 (s, 3 H), 1.08 (s, 3 H), 1.04 (s, 6 H), 0.94 (s, 3 H), 0.62 (s, 3 H); $[\alpha]^{24}_D$ = +45.9 (c = 0.024 in CH_2Cl_2).

Anal. Calcd for $C_{25}H_{38}O$: C, 84.69; H, 10.79. Found: C, 84.65; H, 11.05.

***l*-4,4,14-Trimethyl-13α,14β,17α-pregn-8-ene-3,20-dione (*l*-30).** Ozone was bubbled through a solution of compound **36** (0.170 g, 0.48 mmol) in dichloromethane/methanol (4:1, 20 mL) containing pyridine (0.15 mL) at −78 °C until the reaction was complete as judged by TLC analysis. Triphenylphosphine (0.126 g, 0.48 mmol) was added and the solution allowed to warm to room temperature. Solvent was evaporated and the residue was chromatographed on silica gel (4:1 hexane–ethyl acetate) to give dione ***l*-30** (0.133 g, 78% yield) as a colorless solid, VPC (15 m, 220 °C, 3.82 min, 97%), mp 149–150 °C: IR ($CDCl_3$) 3.38, 5.86, 6.85, 7.24, 7.34, 8.27, 8.47, 8.93 μm; ^{1}H NMR 2.86 (t, 1 H, J = 7.9 Hz), 2.54 (ddd, 1 H, J = 15.9 Hz, J = 9.8 Hz, J = 7.4 Hz), 2.44 (dq, 1 H, J = 15.9 Hz, J = 4.1 Hz), 2.30 (m, 1 H), 2.10 (s, 3 H), 1.98 (m, 3 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 1.04 (s, 3 H), 0.96 (s, 3 H), 0.66 (s, 3 H); EIMS m/z calcd 356.2715, found 356.2719; $[\alpha]^{24}_D$ = −12.8° (c = 0.021 in CH_2Cl_2).

Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.17. Found: C, 80.50; H, 10.35.

20-Hydroxy-24,24-(1,3-propylenedioxy)-5α,13α,14β,17α-lanost-8-en-3-one (37). To a solution of dione ***l*-30** (0.100 g, 0.28 mmol) in toluene (8 mL) at 0 °C was added 2-(2-(bromomagnesio)ethyl)-1,3-dioxane in tetrahydrofuran (0.49 mmol). After 30 min, saturated ammonium chloride was added and the mixture was extracted with ether,[27] giving a colorless oil. Chromatography on silica gel (1:1 hexane–ethyl acetate) provided unreacted dione ***l*-30** (0.15 g, 15% yield) and hydroxy ketone **37** (0.93 g, 70% yield) as a colorless solid, mp 116–117 °C: IR (film) 2.86, 3.35, 5.85, 6.82, 7.22, 8.67, 9.90 μm; ^{1}H NMR 4.49 (t, 1 H, J = 6 Hz), 4.07 (dd, 2 H, J = 12 Hz, J = 6 Hz), 3.74 (dt, 2 H, J = 12 Hz, J = 1.2 Hz), 2.50 (m, 2 H), 1.23 (s, 3 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.90 (s, 3 H), 0.88 (s, 3 H); EIMS m/z calcd 472.3552, found 472.3562.

Preparation of Olefins 38a,b. Methanesulfonyl chloride (53 μL, 0.69 mmol) and diisopropylethylamine (220 μL, 1.26 mmol) were added to a solution of alcohol **37** (0.297 g, 0.63 mmol) in dichloromethane (5 mL) at 0 °C. The progress of the reaction was followed by TLC analysis and additional aliquots of the reagents were added (typically 2 or 3 times) until the reaction was complete. Water was added and the mixture was extracted with ether,[27] giving an oil. Chromatography on silica gel impregnated with 10% silver nitrate (5:1 hexane–ethyl acetate) provided an inseparable mixture of olefins **38a,b**, VPC (15 m, 290 °C, 9.08 min, 9.30 min) (1:1), as a colorless oil that slowly solidified, mp 125–128 °C: IR (film) 3.36, 5.85, 6.82, 7.27, 8.00, 8.65, 8.73, 9.85 μm; ^{1}H NMR 5.22 (t, 1 H, J = 5.9 Hz, trisubstituted olefin **38a**), 4.85, 4.81 (s, 2 H, disubstituted olefin **38b**), 4.94 (t, 1 H, J = 5.2 Hz), 4.07 (m, 2 H), 3.73 (t, 2 H, J = 11.7 Hz), 1.61 (s, 3 H, vinyl methyl), 1.07 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.92, 0.91 (s, 3 H), 0.60, 0.56 (s, 3 H); EIMS m/z calcd 454.3447, found 454.3473.

Preparation of Alcohols 39a,b. Sodium borohydride (0.030 g, 0.78 mmol) was added to a solution of ketones **38a,b** (0.176 g, 0.39 mmol) in methanol (6 mL) at room temperature. After 5 min the hydride was quenched with acetic acid and the mixture was extracted with ether[27] to give alcohols **39a,b** (0.156 g, 88% yield) as a colorless solid, mp 179–181 °C: VPC (15 m, 290 °C, 8.75 min, 8.97 min); IR ($CDCl_3$) 3.38, 6.85, 7.25, 8.03, 8.69, 8.79 μm; ^{1}H NMR 5.22 (t, 1 H, J = 6 Hz, trisubstituted olefin **39a**), 4.85, 4.81 (s, 2 H, disubstituted olefin **39b**), 4.52 (t, 1 H, J = 5.2 Hz), 4.07 (m, 2 H), 3.74 (t, 2 H, J = 11 Hz), 3.22 (m, 1 H), 2.45 (q, 1 H, J = 7.7 Hz), 2.35 (t, 1 H, J = 6 Hz), 1.62 (s, 3 H, vinyl methyl), 0.98 (s, 3 H), 0.93 (s, 3 H), 0.90, 0.89 (s, 3 H), 0.79 (s, 3 H), 0.60, 0.57 (s, 3 H).

***d*-3β-Hydroxy-24,24-(1,3-propylenedioxy)-5α,13α,14β,-17α,20αH-lanost-8-ene (40) and *d*-3β-Hydroxy-24,24-(1,3-propylenedioxy)-5α,13α,14β,17α-lanost-8-ene (41).** A rapidly stirring solution of olefins **39a,b** (0.156 g, 0.34 mmol) in ethyl acetate (6 mL) containing 5% platinum on carbon (15 mg) was placed under 1 atm of hydrogen. TLC analysis using silver nitrate impregnated silica gel showed that the reaction was complete after 6.5 h. The mixture was filtered through Celite using ethyl acetate and the solvent was evaporated under reduced pressure to give a colorless foam. Chromatography on silica gel (7:1 hexane–ethyl acetate) gave two compounds. Alcohol **40** (96.4 mg, 62% yield) as a colorless solid: VPC (15 m, 290 °C, 9.37 min), mp 115–116 °C: IR ($CDCl_3$) 2.76, 3.37, 3.47, 6.82, 7.24, 7.87, 8.66 μm; ^{1}H NMR 4.45 (t, 1 H, J = 5.2 Hz), 4.08 (dd, 2 H, J = 11.8 Hz, J = 4.8 Hz), 3.73 (dt, 2 H, J = 12.2 Hz, J = 2.4 Hz), 3.21 (5-line m, 1 H, J = 4.0 Hz), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.87 (d, 3 H, J = 6.1 Hz), 0.83 (s, 3 H), 0.77 (s, 3 H), 0.72 (s, 3 H); EIMS m/z calcd 458.3760, found 458.3752; $[\alpha]^{21}_D$ = +4.9° (c = 0.015 in chloroform).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.56; H, 10.98. Found: C, 78.75; H, 11.21.

Alcohol **41** (53.0 mg, 34% yield) as a colorless oil: VPC (15 m, 290 °C, 8.28 min), IR ($CDCl_3$) 3.37, 3.47, 6.85, 7.24, 7.86, 9.51 μm; ^{1}H NMR 4.45 (t, 1 H, J = 5.2 Hz), 4.08 (dd, 2 H, J = 10.9 Hz, J = 5.1 Hz), 3.73 (t, 2 H, J = 11.9 Hz), 3.21 (d, 1 H, J = 10.8 Hz), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.84 (s, 3 H), 0.81 (d, 3 H), J = 6.1 Hz), 0.77 (s, 3 H), 0.73 (s, 3 H); EIMS m/z calcd 458.3760, found 458.3758; $[\alpha]^{25}_D$ = +21.0 (c = 0.0054 in chloroform).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.56; H, 10.98. Found: C, 78.70; H, 11.25.

***d*-3β-Hydroxy-5α,13α,14β,17α,20αH-lanost-8-en-24-al (42).** Aqueous hydrochloric acid (2.5%, 1.5 mL) was added to a solution of acetal **40** (27.5 mg, 0.060 mmol) in tetrahydrofuran (6 mL) and the solution was heated at reflux for 3 h. The solution was cooled to room temperature and extracted[27] with ether to give a colorless solid. Chromatography on silica gel (5:1 hexane–ethyl acetate)

gave aldehyde **42** as a colorless solid (14 mg, 58%), VPC (15 m, 290 °C, 5.01 min), mp 160–162 °C: IR ($CDCl_3$) 2.76, 3.38, 3.64, 5.80, 6.87, 7.25 μm; ^1H NMR 9.75 (t, 1 H, J = 1.9 Hz), 3.22 (m, 1 H), 2.40 (m, 2 H), 0.98 (s, 3 H), 0.93 (s, 3 H), 0.88 (d, 3 H, J = 5.9 Hz), 0.85 (s, 3 H), 0.77 (s, 3 H), 0.73 (s, 3 H); EIMS m/z calcd 400.3341, found 400.3350; $[\alpha]^{25}_D$ = +0.56° (c = 0.0070 in chloroform). This aldehyde as well as its C-20 epimer **43** was oxygen sensitive and satisfactory combustion analyses were not obtained.

Preparation of *d*-Tirucallol (1c). *n*-Butyllithium (44 μL, 0.087 mmol) was added to a slurry of isopropyltriphenylphosphonium iodide (38 mg, 0.087 mmol) in tetrahydrofuran (1 mL) at 0 °C. After 10 min at 0 °C, tris[2-(2-methoxyethoxy)ethyl]amine (4 μL, 0.003 mmol) was added, followed by addition of aldehyde **42** in tetrahydrofuran (0.5 mL). After 10 min at 0 °C, acetone was used to destroy excess ylide and the solvent was removed under reduced pressure. Chromatography on silica gel (3:1 hexane–ether) provided *d*-tirucallol (**1c**) as a colorless solid (11 mg, 74% yield), VPC (50 m, 280 °C, 9.86 min), mp 130–131 °C: IR ($CDCl_3$) 2.76, 3.38, 3.47, 6.85, 7.24, 8.03, 8.66 μm; ^1H NMR 5.07 (t, 1 H, J = 6.9 Hz), 3.22 (5-line m, 1 H, J = 6.1 Hz), 2.06 (m, 3 H), 1.90 (m, 3 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 0.98 (s, 3 H), 0.93 (s, 3 H), 0.89 (d, 3 H, J = 6.3 Hz), 0.84 (s, 3 H), 0.78 (s, 3 H), 0.73 (s, 3 H); EIMS m/z calcd 426.3861, found 426.3862; $[\alpha]^{26}_D$ = +4.1° (c = 0.0083 in benzene).

Anal. Calcd for $C_{30}H_{50}O$: C, 84.45; H, 11.80. Found: C, 84.34; H, 12.09.

***d*-3β-Hydroxy-5α,13α,14β,17α-lanost-8-en-24-al (43).** The hydrolysis of acetal **41** was performed as described for the hydrolysis of acetal **40** except chromatography was not required to purify aldehyde **43** (43.5 mg, 94%), a colorless foam by VPC (15 m, 290 °C, 4.34 min): IR (film) 2.91, 3.38, 3.45, 3.65, 5.78, 6.82, 7.22, 9.05, 9.66 μm; ^1H NMR 9.76 (t, 1 H, J = 1.8 Hz), 3.21 (dd, 1 H, J = 11.6 Hz, J = 4.6 Hz), 2.40 (m, 2 H), 0.98 (s, 3 H), 0.93 (s, 3 H), 0.86 (s, 3 H), 0.82 (d, 3 H, J = 5.9 Hz), 0.78 (s, 3 H), 0.75 (s, 3 H); EIMS m/z calcd 400.3341, found 400.3331; $[\alpha]^{25}_D$ = +25.3° (d = 0.017 in chloroform).

Preparation of *d*-Euphol (1a). *d*-Euphol (**1a**) was synthesized by Wittig olefination of aldehyde **43** as described for the synthesis of *d*-tirucallol (**1c**), providing a colorless solid (22.3 mg, 70% yield) that produced colorless needles from acetonitrile, mp 119–120 °C; VPC (15 m, 290 °C, 4.47 min): IR ($CDCl_3$) 2.76, 3.38, 3.47, 6.87, 7.26, 8.97, 9.11, 9.76 μm; ^1H NMR 5.07 (t, 1 H, J = 7.1 Hz), 3.21 (dd, 1 H, J = 11.6 Hz, J = 5.5 Hz), 2.05 (m, 2 H), 1.88 (m, 4 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 0.98 (s, 3 H), 0.93 (s, 3 H), 0.85 (s, 3 H), 0.83 (d, 3 H, J = 6.2 Hz), 0.77 (s, 3 H), 0.73 (s, 3 H); $[\alpha]^{25}_D$ = +31.0° (c = 0.0104, $CHCl_3$); EIMS m/z calcd 426.3861, found 426.3868.

Anal. Calcd for $C_{30}H_{50}O$: C, 84.45; H, 11.80. Found: C, 84.43; H, 12.07.

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Registry No. **1a**, 514-47-6; **1c**, 514-46-5; (±)-**7**, 124718-18-9; (±)-**8**, 124718-19-0; (±)-**9**, 124718-20-3; (±)-**10**, 124718-21-4; **11**, 513-81-5; **12**, 53060-22-3; **13**, 3780-51-6; **16**, 124718-22-5; **18**, 124718-23-6; **19**, 124718-24-7; **20**, 28333-62-2; **21**, 124718-25-8; **22**, 124718-26-9; **23**, 124718-27-0; (±)-**24** (isomer 1), 124718-28-1; (±)-**24** (isomer 2), 124718-44-1; (±)-**25** (isomer 1), 124718-29-2; (±)-**25** (isomer 2), 124718-45-2; (±)-**26** (isomer 1), 124718-30-5; (±)-**26** (isomer 2), 124718-46-3; (±)-**27** (isomer 1), 124718-31-6; (±)-**27** (isomer 2), 124718-47-4; (±)-**28** (isomer 1), 124718-32-7; (±)-**28** (isomer 2), 124718-48-5; (±)-**29** (isomer 1), 124718-33-8; (±)-**29** (isomer 2), 124718-49-6; (±)-**30**, 124816-95-1; *l*-**30**, 124816-99-5; **31**, 14495-28-4; **32**, 13879-04-4; **33**, 88199-56-8; **34**, 124718-34-9; **35**, 124754-15-0; **36**, 124718-35-0; **37**, 124718-36-1; **38a**, 124718-42-9; **38b**, 124718-37-2; **39a**, 124718-43-0; **39b**, 124718-38-3; **40**, 124718-39-4; **41**, 124816-96-2; **42**, 124816-97-3; **43**, 124816-98-4; I, 43001-29-2; II, 124718-41-8; IV, 5217-14-1; CH_2=C=CH_2, 463-49-0; (±)-CH_2=$C(CH_3)C(CH_3)CH_2Cl(OBu\text{-}t)$, 124718-40-7; euphorbyl acetate, 14787-39-4.

Extraction of Alkanol Isomers

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The isomer effects on the equilibrium partition coefficients of the two propanol, the four butanol, and two of the pentanol isomers between water and immiscible solvents are shown to be governed primarily by the abilities of the alkanols to donate and accept hydrogen bonds. These abilities depend directly on the number of methyl groups bonded to the carbon atom that carries the hydroxyl group. The overall partition coefficient, irrespective of the isomeric form, depends on the total number of carbon atoms in the alkanol via its molar volume. The dependencies on the natures of the extracting solvents are also rationalized in terms of their cohesive energy density, their polarity and polarizability, and their hydrogen bond donation and acceptance abilities.

In a recent paper, Arenson, Kertes, and King[1] reported on the distribution of the four butanol isomers between solutions of *m*-cresol in *n*-octane and water. They discussed the effect of the isomeric form of the butanol on the hydrogen-bond formation between it and the *m*-cresol. They also showed a table of the partition coefficients of the butanol isomers between certain organic solvents and water, in which a systematic decrease of these coefficients for a given solvent in the sequence *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl alcohol is observed. However, they did not discuss this sequence in the absence of *m*-cresol.

Kertes and King in their review[2] reported the partition coefficients of additional lower alkanols between organic solvents and water, so that a body of data exists that can be interpreted in terms of the isomeric effects for alkanol distribution in general. The distribution of organic solutes between 1-octanol and water in terms of a general linear

(1) Arenson, D. R.; Kertes, A. S.; King, C. J. *J. Solution Chem.* **1988**, *17*, 1119.

(2) Kertes, A. S.; King, C. J. *Chem. Rev.* **1987**, *87*, 687.

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