11%) of the trans isomer (**6b**): mp 126–130 °C dec; IR (CCl_4) 1720 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 6.8–7.8 (m, 20 H), 4.27 (s, 1 H), 3.07 (s, 3 H); M_r found (mass spectrometry) 416. Anal. Calcd for $C_{30}H_{24}O_2$: C, 86.51; H, 5.81. Found: C, 86.62; H, 6.04.

1,3-Dimethoxy-1,2,4,5-tetraphenyl-2,4-cyclopentadiene (9). The procedure used for the preparation of this compound was exactly the same as that described for **5b** to the point of stirring at 27 °C for 50 min. At the end of this time, 2 mL of methyl iodide were added to the deep red solution of enolate **4b** which was then stirred at 27 °C for an additional 45 min. The contents of the flask were then transferred to a separatory funnel containing 50 mL of water, and the benzene layer was separated, washed twice with 50-mL portions of water, and dried over magnesium sulfate. Removal of the solvent on a rotary evaporator afforded a dark red oil which was dissolved in 20 mL of absolute ethanol. The crystals obtained were filtered and washed with cold 95% ethanol affording 1.77 g (4.1 mmol, 79%) of impure material which upon recrystallization from absolute ethanol produced 1.70 g of dazzling yellow needles: mp 160–161 °C; IR (CCl_4) 1650 (C=$COCH_3$), 1085 (COC) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.9–7.6 (m, 20 H), 3.51 (s, 3 H), 3.32 (s, 3 H); M_r found (mass spectrometry) 430. Anal. Calcd for $C_{31}H_{26}O_2$: C, 86.48; H, 6.09. Found: C, 86.31; H, 6.23.

Tables I–III. The data reported in the tables were obtained using the following procedures.

Formation of Enolate 4a. Into a 25-mL three-necked flask equipped with a magnetic stirrer was placed 100 mg of tetracyclone (1), 25 mg of potassium cyanide, 7.5 mL of benzene, and 7.5 mL of Me_2SO (or 15 mL of *N,N*-dimethylformamide) and the reaction was stirred at 27 °C for 3 h.

Formation of Enolate 4b. Into a 25-mL three-necked flask equipped with a magnetic stirrer was placed 100 mg of tetracyclone (1), 7.5 mL of benzene, and 7.5 mL of Me_2SO. To this solution was added 0.2 mL of Triton B (or 0.25 mL of 1.2 M potassium methoxide in methanol) and the resulting solution was stirred at 27 °C for 15 min.

Kinetic Protonation of Enolates 4a and 4b. Approximately 5 min prior to protonation, the temperature of the flask containing the enolate was adjusted to the desired level (0 °C by using an ice bath or 90 °C by refluxing the solvent) and at this point, 5 drops of concentrated HCl was rapidly added. The flask contents were then transferred to a separatory funnel containing 10 mL of benzene and 10 mL of water, and the benzene layer was separated, washed twice with 20-mL portions of water, and dried over anhydrous magnesium sulfate. Removal of the solvent with a rotary evaporator afforded a yellow oil which was dissolved entirely in $CDCl_3$ and analyzed by ^1H NMR. The cis–trans ratios were determined by proton integration and recorded in Table I.

Quenching Enolate 4a with Methyl Iodide. At the temperatures specified in Table III, 1 mL of methyl iodide was added to the enolate **4a** and the resulting solution was stirred for 10 min. The remaining purification procedure was identical with that described above.

Equilibration of Isomers 5 and 6. Into a 25-mL three-necked flask equipped with a magnetic stirring bar was placed 100 mg of the starting isomer (either **5** or **6**), 7.5 mL of benzene, and 7.5 mL of Me_2SO. Once the sample had dissolved (ca. 5 min), the particular isomerization mode was employed: (a) Base (for **5a** and **6a**). One drop of a saturated solution of potassium cyanide in Me_2SO was added to the above mixture, the solution was stirred at 27 °C for the amount of time indicated in Table II, and then the solution was analyzed by ^1H NMR. (b) Base (for **5b** and **6b**). One drop of a base solution, prepared by adding 5 drops of Triton B to 1 mL of Me_2SO, was added to the above solution to be equilibrated, the solution was stirred at 27 °C for 2 h, and the solution was analyzed by ^1H NMR to give the results recorded in Table II. (c) Acid. Three drops of concentrated HCl were added to the above solution to be equilibrated and the solution was stirred at the temperature and for the time indicated in Table II. Analysis of the resulting solution by ^1H NMR afforded the results recorded. (d) Thermal. Refluxing the solution at 90 °C for the time specified in Table II, followed by ^1H NMR analysis of the resulting solution, afforded the results recorded.

Registry No. 1, 479-33-4; **4a**, 92011-29-5; **4b**, 92011-30-8; **5a**, 92011-31-9; **5b**, 58008-91-6; **6a**, 92011-32-0; **6b**, 58009-01-1; **7**, 92011-33-1; **8**, 92011-34-2; **9**, 92011-35-3.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **6a** and **7** (12 pages). Ordering information is given on any current masthead page.

Photochemical Synthesis of Decipiene Diterpenes

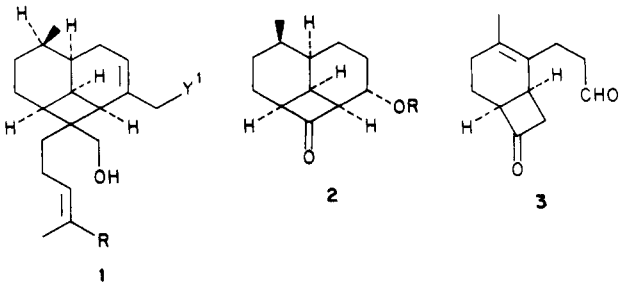
William G. Dauben* and Gideon Shapiro

Department of Chemistry, University of California, Berkeley, California 94720

Received March 6, 1984

The decipiene diterpene nucleus has been synthesized by an intramolecular [2 + 2] photocycloaddition between an enone and an allene grouping. The process makes use, for the first time, of a stereocontrol element at a remote center in the precursor unit to control the final stereochemistry of the product. A formal total synthesis of (±)-trihydroxydecipiadiene has been achieved.

The decipiane diterpenoids **1**, a new class of diterpenes isolated[1] from the surface coating of *Eremophilia decipiens*, contain the tricyclo[5.3.1.$0^{5,11}$]undecane ring skeleton; the CH_2Y^1 can be a primary alcohol or a methyl group and R can be a primary alcohol or a carboxyl group. A total synthesis of (±)-trihydroxydecipiadiene (**1**, Y^1 = OH, R = CH_2OH) has been reported,[2] a synthetic route which



first prepared the basic tricyclic skeleton **2** by cyclization of **3**. The elaboration of the side chain was performed in

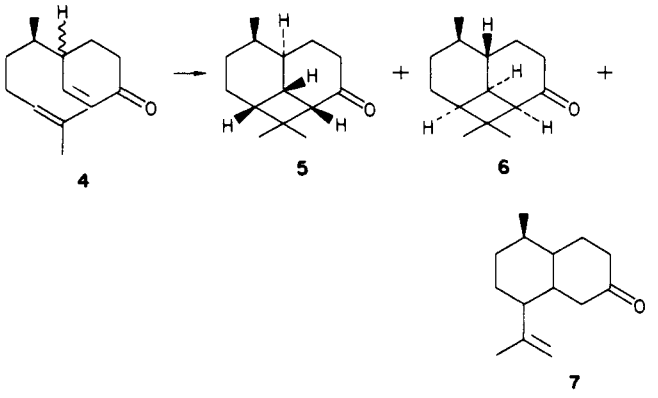
(1) (a) Ghisalberti, E. L.; Jefferies, P. R.; Sheppard, P. *Tetrahedron Lett.* **1975**, 1775. (b) Maslen, E. N.; Sheppard, P. N.; White, A. H.; Willis, A. C. *J. Chem. Soc. Perkin Trans. 2* **1976**, 263. (c) Ghisalberti, E. L.; Jefferies, P. R.; Sheppard, P. N. *Tetrahedron* **1980**, *36*, 3253. (d) Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Marshall, D. G.; Raston, C. L.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 1529. (e) Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Stuart, A. D. *Tetrahedron* **1981**, *37*, 383. (f) Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Stuart, A. D.; Raston, C. L.; White, A. H. *J. Chem. Soc. Perkin Trans. 2* **1981**, 1473.

(2) Greenlee, M. L. *J. Am. Chem. Soc.* **1981**, *103*, 2425.

0022-3263/84/1949-4252$01.50/0

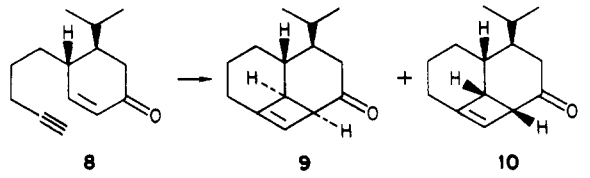
a straightforward manner via the Trost spiroannelation procedure.[3]

The tricyclo[5.3.1.0^{5,11}]undecane ring skeleton of the decipianes seemed well suited to construction by an intramolecular [2 + 2] photocycloaddition of a 1,7-diene. In 1981, Jefferies[1] reported a model photochemical study using the α,β-unsaturated ketone **4**. The two cycloaddition



4 **5** **6** **7**

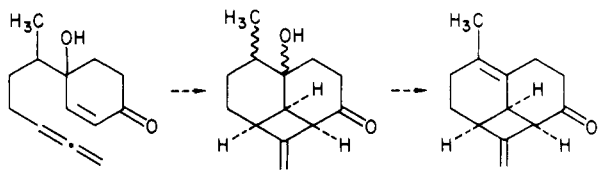
products **5** and **6** obtained were shown by X-ray analysis to possess the desired tricycloundecane ring system but to possess the trans-A/B-ring juncture rather than the cis-ring juncture present in the natural decipiane diterpenes. In addition, an equal amount of bicyclic enone **7** was formed, a product often found with the olefin structure utilized. Recently, Smith[4] has shown that



8 **9** **10**

photochemical addition of the acetylenic ketone **8** gave a 1.5:1 ratio of trans adduct **9** to cis adduct **10**. It is evident that in its simplest form, this [2 + 2] photocycloaddition is not suited for an efficient synthesis of the decipienes.

To overcome this apparent preference for the formation of the unnatural *trans*-decalin stereochemistry, it is obviously necessary to incorporate a stereochemical element which will allow entry into the natural skeleton. Such can readily be achieved, in theory, by substitution of a hydroxyl group for the hydrogen atom at the 4-position of the cyclohexenone. Photocycloaddition of a 4-hydroxyl-substituted enone system **11**, such a unit not having been studied



11 **12** **13**

previously, to yield adduct **12** followed by dehydration to **13** and hydrogenation from the convex face of this molecule would give the desired skeleton related to **2**. Modification of the exocyclic methylene group can be done at the appropriate time.

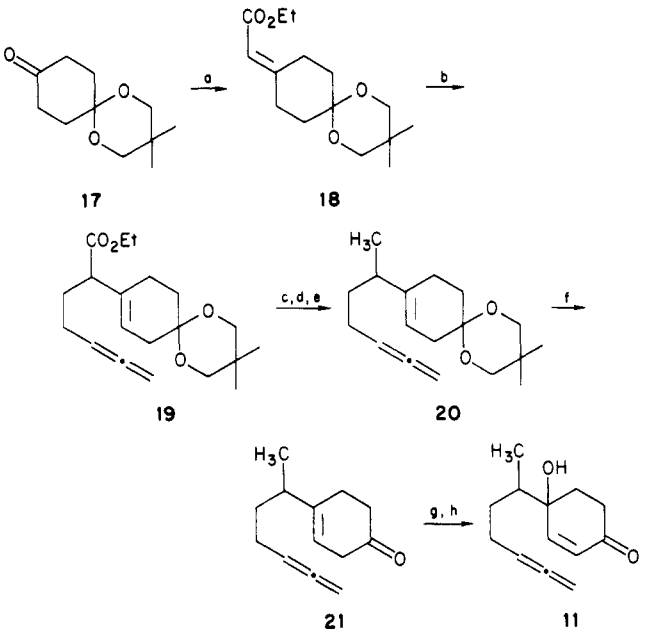
As shown in Scheme I, one of the starting materials needed was the known 1-iodo-3,4-pentadiene (**16**)[5] but in this study it was prepared in a more convenient manner. The known allenic ester **14**,[6] prepared by reaction of propargyl alcohol with triethyl orthoacetate, was reduced with LAH at −78 °C to 0 °C to give the alcohol **15** in 70% yield.

$$=\cdot=\underset{\mathbf{14}}{-CH_2CO_2Et} \rightarrow =\cdot=\underset{\mathbf{15}}{-CH_2CH_2OH} \rightarrow =\cdot=\underset{\mathbf{16}}{-CH_2CH_2I}$$

When this reduction was conducted at 0 °C, a mixture of dienic products, resulting from deprotonation of the activated methylene group followed by kinetic protonation, was obtained. A similar result has been reported in the LAH reduction of ethyl trideca-3,4-dienoate.[7] In this case, as in the present work, the reduction difficulties could be circumvented by the use of Dibal. However, for large-scale reactions the low temperature LAH reduction is clearly more convenient. In the earlier preparation, the iodide **16** was prepared using triphenyl phosphite methiodide in Me_2SO in a 25% yield. This conversion is more conveniently done in higher yield by conversion of **15** to the mesylate ester using mesyl chloride and triethylamine followed by sodium iodide in acetone, the yield being 75%.

The synthesis of the starting material **11** for the photochemical ring closure is outlined in Scheme I. The monoketal of 1,4-cyclohexanedione **17**[8] was converted to the unsaturated ester **18** in 92% yield using the Wadsworth–Emmons reaction. The enolate of this ester, prepared using LDA–HMPA in THF, was alkylated with the iodide to give **19** in 74% yield. The ester grouping of **19** was reduced with LAH, and the alcohol converted to the mesylate ester which was reduced with lithium triethylborohydride to yield **20** in 66% yield in the three-step sequence.[9] The ketal was carefully hydrolyzed with 1 N

Scheme I[a]



17 **18** **19** **20** **21** **11**

[a] (a) $(EtO)_2POCH_2CO_2Et$; (b) LDA–HMPA, THF; $=\cdot=-CH_2CH_2I$; (c) LAH; (d) MsCl, Et_3N; (e) $LiEt_3BH$; (f) 1 N HCl, THF; 25 °C; (g) MCPBA, $NaHCO_3$; (h) K_2CO_3, MeOH.

(3) (a) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3080. (b) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *Ibid.* **1977**, *99*, 3088.

(4) Koft, E. R.; Smith, A. S., III *J. Am. Chem. Soc.* **1982**, *104*, 5568; *Ibid.* **1981**, *106*, 2115.

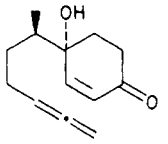
(5) Sherrod, S. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 1925.

(6) Crandall, J. K.; Tindell, G. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1411.

(7) Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 353.

(8) Marshall, J. A.; Flynn, G. A. *Synthetic Comm.* **1979**, *9*, 123. This ketal was prepared using the procedure reported to synthesize the 1,4-butanediol ketal: Hyatt, S. A. *J. Org. Chem.* **1983**, *48*, 129.

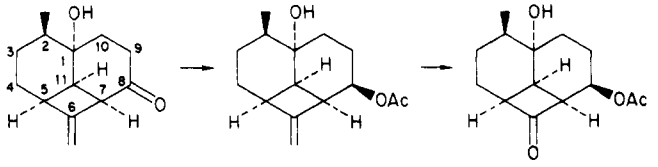
hydrochloric acid in THF (25 °C, 48 h) to give the β,γ-unsaturated ketone **21** which was chemoselectively epoxidized under buffered, two-phase reaction conditions.[10] The sensitive epoxide was immediately treated with K_2CO_3–MeOH to give the desired γ-hydroxy-α,β-unsaturated ketone **11** in a yield of 44% over the two steps. The diastereomeric mixture of **11** could not be separated by capillary gas chromatography. The mixture was analyzed by ^1H NMR spectroscopy; the methyl doublets were readily resolved and indicated a 60:40 ratio of diastereomers. The major isomer can be assigned structure **11a**



11a

since the structure of this isomer may be correlated with that of a later intermediate whose structure was determined by X-ray crystallographic analysis.

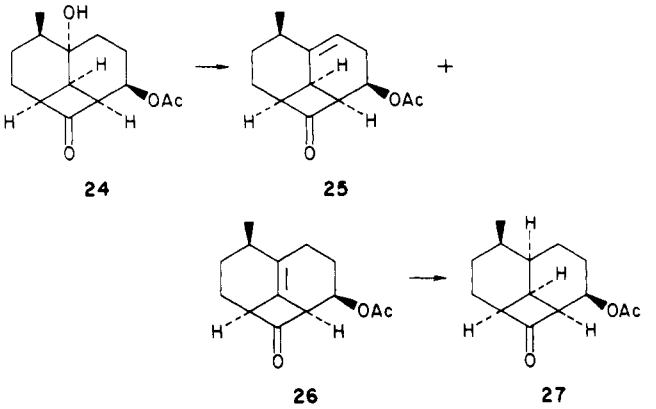
A 6.7 mM solution of the diastereomeric mixture **11** in dry ether was irradiated at −70 °C through a uranium glass filter with a 450-W Hanovia lamp until all the starting material had reacted. The mixture was analyzed by capillary gas chromatography and showed one major product (60% yield) and three minor products (11%, 5%, and 16%, listed in order of retention times). The major product was isolated by column chromatography and shown to have structure **22** by further transformations. The isolated photoproduct was reduced with L-Selectride, and the resulting alcohol selectively acetylated to give **23** (31% from **22**). The olefin was converted to the crystalline ketone



22 **23** **24**

24 (mp 155–156 °C, ether–hexane) by osmylation and lead tetraacetate glycol cleavage in 48% yield. This crystalline material was subjected to X-ray crystallographic analysis and shown to possess structure **24** (Figure 1).[11] It is to be noted that in this case the decalin ring fusion is cis. The methyl group is trans to the tertiary hydroxyl function placing it in the natural configuration of the decipiane diterpenes.

The alcohol **24** was dehydrated with $POCl_3$·DMAP (0–20 °C) to give a mixture of equal amounts of the two olefins **25** and **26**, the composition determined by ^1H NMR analysis.[12,13] The crude olefin mixture was hydrogenated

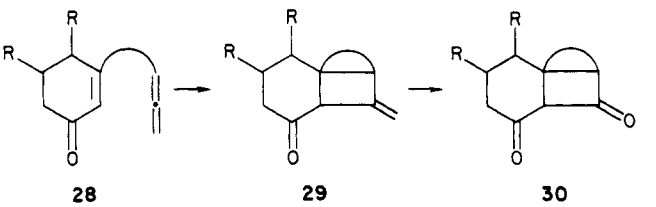


24 **25** **26** **27**

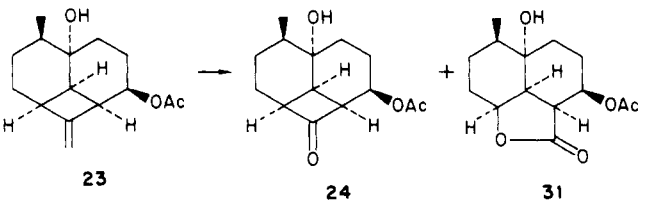
in ethyl acetate using Pd·Al_2O_3 catalyst to give a single crystalline isomer **27** (mp 95–97 °C, ether–hexane) in a 95% overall yield from **24**. This isomer is the epimeric acetate to that synthesized by Greenlee.[14] The ^1H NMR spectrum of **27** is essentially identical to the previously synthesized **2** (R = Ac)[14] except the carbinyl proton is a doublet of triplets while in **2** it is a doublet of doublets.

The stereochemistry of the acetate function is of no consequence as the center is destroyed later in the total synthesis.[2] This photochemical approach using a stereocontrol element constitutes a formal total synthesis of trihydroxydecipiadiene.

In the course of this synthesis, the degradation of the methylenecyclobutene derivative **23** and the dehydration of the tertiary alcohol derivative **24** gave results which warrant further discussion. The intramolecular photocycloaddition reaction of a compound with the general structure **28** containing a terminal allene linked by a hydrocarbon chain to a cyclohexenone has been extensively studied.[15] The major, if not the sole, route is the head-to-head photocycloaddition to yield a compound as **29**. These methylenecyclobutene derivatives have been readily converted into cyclobutanones as **30**, by ozonization in CH_2Cl_2 at −78 °C, followed by addition of dimethyl sulfide at −78 °C.



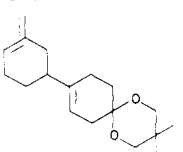
28 **29** **30**



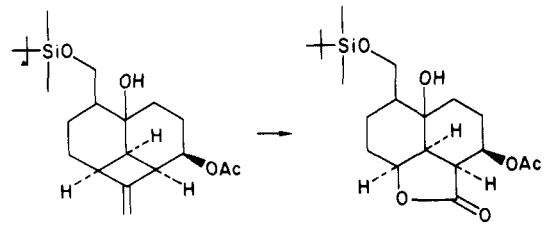
23 **24** **31**

When **23** was ozonized under the above conditions, a 1:1 mixture of the cyclobutanone **24** and the lactone **31** was obtained in a total yield of 40%, after chromatography. When the *tert*-butyldimethylsiloxy compound **32**, related to **23**, was ozonized under the same conditions, only the lactone **33** was obtained. This type of Baeyer–Villiger reaction has been previously encountered in the ozonation of a methylene group on a rigid structure.[16]

(9) When the corresponding iodide was allowed to react with tributyltin hydride, only cyclization involving the allene occurred to yield compounds of the following type.



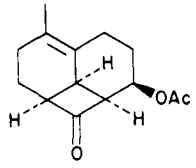
(10) Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267.
(11) Analysis performed by Dr. F. Hollander, University of California, Berkeley, X-ray Crystallographic Facility (CHEXRAY).
(12) A trace of a third olefin was present and most likely is the third nonrearranged isomer expected from the dehydration.
(13) When the dehydration was conducted with the Burgess reagent (Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26), the ratio of the two main products was changed to 1.2:1.
(14) A spectrum of **2** (R = Ac) was kindly supplied by Dr. Greenlee.
(15) (a) Becker, D.; Harel, Z.; Nagler, M.; Gillon, A. *J. Org. Chem.* **1982**, *47*, 3297 and references cited therein. (b) McKay, W. R.; Ounsworth, J.; Sum, P-E.; Weiler, L. *Can. J. Chem.* **1982**, *60*, 872.



32 33

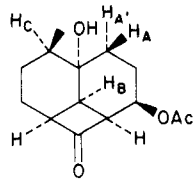
In line with the accepted mechanistic concept of the ozonation reaction, a solvent dependence has been found. When **23** was ozonized in methanol a variety of products were obtained in low yield; **32** upon ozonation in methanol gave a 1:1 mixture of ketone and lactone in a 40% yield. In this latter case, no ketone was obtained in CH_2Cl_2 solution. The difference in this present case as compared to the earlier use of this degradation method on methylenecyclobutene derivatives may be related to the rigidity and/or strain at the ring system. The influence of the silyl ether on the course of the reaction is not obvious.

As mentioned earlier, the dehydration of the alcohol **24** with $POCl_3$·DMAP (0–20 °C) gave a mixture of equal amounts of the two olefins **25** and **26**, with a trace of a third olefin postulated to be **34**. That the composition of this



34

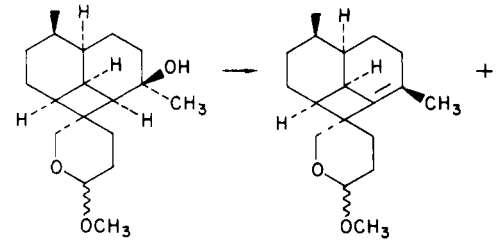
mixture did not represent the relative thermodynamic stability of the three olefins was shown by transformation of the mixture mainly of **25** and **26** with a catalytic amount of *p*-toluenesulfonic acid in refluxing chloroform to a mixture of **25** and **34**. When alcohol **24** was dehydrated with $SOCl_2$·DMAP, a similar mixture of **25** and **26** was obtained. The formation of the exocyclic methylenecyclobutane **26** formally arises from a syn elimination. When the structural parameters obtained from the crystal structure studies of **24** the dihedral angles relationship



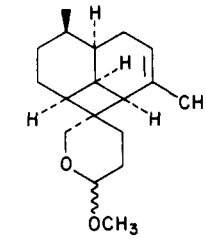
24

between the hydroxy group and H_A, H_A', H_B, and H_C are 176°, 57°, 19°, and 51°, respectively. In this structural arrangement, H_A is closer to being antiperiplanar with the hydroxyl group than the other hydrogen atoms in position for elimination and such a steric arrangement would favor elimination of H_A on stereoelectronic grounds. Thus, a simple E2 type of elimination mechanism cannot be the sole functioning process in this system. The near syn-coplanar arrangement of H_B and the hydroxyl group speak for a syn elimination pathway competing with an anti elimination pathway in the elimination process.

It is of interest to note in the Greenlee synthesis[2] the dehydration of the tertiary alcohol **35** with $POCl_3$·DMAP in pyridine gave a 4:1 mixture of olefins **36** and **37**. The instability of the methylenecyclobutane derivative **36** was



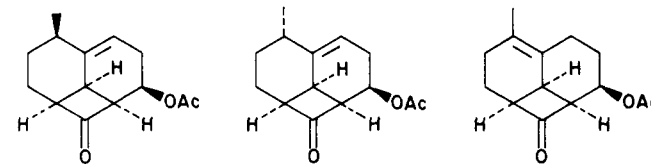
35 36



37

demonstrated by complete isomerization to the trisubstituted olefin **37** with sulfur dioxide in chloroform.[17] In this case, the methylenecyclobutane compound arises via a formal anti elimination. The results of these two studies suggest that the cyclobutyl proton removal is a kinetically favorable process which may be related to an enhanced acidity of such a proton.

To evaluate in more detail the thermodynamic relationship between the three isomeric olefins **25**, **26**, and **34** studied in the present work, the 1:1 mixture of **25** and **26**,



25 38 34

with a trace of **34**, was allowed to react with liquid sulfur dioxide in a sealed NMR tube. The reaction product was a 45:45:10 mixture of **25**, **38**, and **34**. Hydrogenation of this mixture gave a 55:45 ratio of **27** and its methyl epimer, in accord with the olefin product ratio.

Again, it was surprising to receive so little of the tetrasubstituted olefin **34** under conditions shown to be equilibrating in view of isomerization of the methyl group. Intrigued by these results which were not intuitively obvious, force field calculations were performed for three olefin structures in order to see if the calculated product stabilities concurred with the experimental product ratios.

Molecular mechanics force field calculations were performed on four conformations of each of the olefins **25**, **34**, and **38**.[18] In each case, proceeding from an initial conformation, separately only the A ring, then only the B ring, and finally both the A and B rings were altered by flipping C-3 and C-4 relative to an axis through C-2 and C-5, by flipping C-8 and C-9 relative to an axis through C-7 and C-10, and finally by a combination of these distortions. In all cases, the acetate was fixed in its lowest energy conformation with the ester carbonyl group eclipsing the C-8–O bond.

The heats of formation calculated for the conformations of each isomeric olefin were averaged in a Boltzmann

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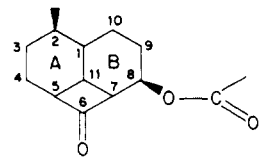

distribution to values of −109.6 kcal mol^{-1}, −108.3 kcal mol^{-1}, and −107.7 kcal mol^{-1} for **34**, **38**, and **25**, respectively. These calculated values would suggest an equilibrium mixture of 87% of **34**, 9% of **38**, and 4% of **26**. Thus, the calculations indicate that the tetrasubstituted olefin isomer **34** is more stable than either trisubstituted olefin isomer **38** or **25**. This discrepancy between the calculated equilibrium distribution (gas phase) and that obtained in the sulfur dioxide equilibrium could be due to the fact that it is the sulfur dioxide complexes of the olefin which were the equilibrium compounds. The earlier study of the rearrangement of **26** to **25** and **34** with *p*-toluenesulfonic acid in chloroform was repeated using a longer heating period, but under these more forcing conditions, extensive decomposition of the compounds occurred and so no equilibration information was obtained.

Experimental Section[19]

Ethyl 3,4-Pentadienoate (14).[6] Triethyl orthoacetate (200 g, 1.23 mol), propargyl alcohol (51 g, 0.91 mol) and 2 mL of propionic acid were heated at 100 °C for 1 h. The ethanol was distilled, and when this distillation stopped, the temperature was raised to 140 °C. More distillate was collected until distillation ceased. The temperature was raised to 180 °C, and the solution was allowed to reflux for 4 h. The solution was cooled to ambient temperature, and 150 mL of THF and 100 mL of 5% HCl were added. The mixture was stirred overnight and was poured into 150 mL of pentane. The aqueous layer was separated, and the organic layer was washed with bicarbonate and brine and dried ($MgSO_4$). The solvents were removed by simple distillation, and the product was distilled to give 26.9 g of a clear oil (24%); bp 65–70 °C (20 mm); IR 3060, 1955, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3, J = 7.1 Hz), 2.99 (d, t, 2, J = 7.0, 3.0 Hz), 4.07 (q, 2, J 7.1 Hz), 4.67–4.73 (d, t, 2, J = 3.0, 7.0 Hz), 5.21 (quintet, 1, J = 7.0 Hz).

3,4-Pentadien-1-ol (15). To a stirred suspension of lithium aluminum hydride (2.85 g, 71 mmol) in 100 mL of ether was added ethyl 3,4-pentadienoate (15.0 g, 120 mmol) in 30 mL of ether at −78 °C. The solution was allowed to warm to room temperature. The solution was stirred for 1 h and saturated aqueous sodium sulfate was added until the aluminum salts began to precipitate. The mixture was filtered and the salts were washed with dichloromethane. The solvents were removed by simple distillation and the resulting oil was distilled to give 7.61 g (75%) of product as a clear oil: bp 60–63 °C (20 mm) (lit.[22] bp 48 °C (10 mm)); IR (3050–3700, 1955 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.14–2.24 (m, 2), 2.45 (s, 1), 3.58–3.65 (m, 2), 4.64 (d, t, 2, J = 3.0, 6.8 Hz), 5.05 (quintet, 1, J = 6.8 Hz).

1-Iodopenta-3,4-diene (16). To a mechanically stirred solution of 3,4-pentadien-1-ol (17.3 g, 0.21 mol) and triethylamine (30.3 g, 0.30 mol) in 300 mL of dichloromethane was added a solution of methanesulfonyl chloride (26.3 g, 0.23 mol) in 80 mL of dichloromethane at −30 °C. Triethylamine hydrochloride began to precipitate and the solution was stirred at −10 °C for 1 h. The mixture was poured into aqueous sodium bicarbonate and the aqueous layer was separated. The organic layer was washed with brine, dried, (Na_2SO_4), and concentrated to 29.0 g of a clear oil. A solution of the mesylate (14.3 g, ca. 80 mmol) and anhydrous sodium iodide (24.0 g, 200 mmol) in 170 mL of acetone was heated at reflux overnight. The reaction mixture was cooled and poured into pentane. This solution was washed with saturated aqueous sodium bisulfite and brine and dried (Na_2SO_4). The solvents were removed by simple distillation and the resulting oil was distilled to give 15.0 g (75% from 3,4-pentadien-1-ol) of product as a clear oil: bp 66–70 °C (20 mm); IR 1955 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44–2.55 (m, 2), 3.14 (t, 2, J = 7.2 Hz), 4.68 (d, t, 2, J = 3.0, 6.6 Hz), 5.06 (quintet, 1, J = 6.6 Hz).

1-(Carbethoxymethylene)cyclohexan-4-one 2,2-Dimethylpropanediyl Ketal (18). To a stirred suspension of hexane washed sodium hydride (2.06 g, 0.043 mol) in 60 mL of DME was added ethyl (diethylphosphinyl)acetate (9.64 g, 0.043 mol) at ice-bath temperature. When the hydrogen evolution had ceased, cyclohexane-1,4-dione 2,2-dimethylpropanediyl monoketal (8.20 g, 0.041 mol)[8] was added in 40 mL of DME at ice-bath temperature. A gummy precipitate formed and the clear solution was stirred an additional hour at room temperature. The solution was poured into saturated ammonium chloride solution and the resulting mixture was extracted with hexane. The combined extracts were dried over magnesium sulfate, concentrated, and distilled to give 10.1 g (92%) of product as a clear oil: bp 127–132 °C (0.07 torr); IR (thin film) 1710, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.61 (s, 1), 4.11 (q, 2, J = 7.2 Hz), 3.51 (d, 2, J = 11.2 Hz), 3.46 (d, 2, J = 11.2 Hz), 2.88 (t, 2, J = 6.4 Hz), 2.27 (t, 2, J = 6.4 Hz), 1.88 (t, 4, J = 6.4 Hz), 1.22 (t, 3, J = 7.2 Hz), 0.96 (s, 3), 0.93 (s, 3). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.01; H, 8.98.

4-(1-Carbethoxy-4,5-hexadienyl)cyclohex-3-enone 2,2-Dimethylpropanediyl Ketal (19). To a stirred solution of diisopropylamine (4.35 g, 43.0 mmol) in 50 mL or THF was added *n*-BuLi (22.0 mL, 1.75 M in hexane, 38.5 mmol) at ice-bath temperature. The solution was stirred for 10 min, cooled to −78 °C, and HMPA (6.20 g, 34.5 mmol) was added. The ester **18** (9.20 g, 34.3 mmol) was added in 20 mL of THF and the solution was stirred for 45 min. 1-Iodo-3,4-pentadiene (7.80 g, 40.0 mmol) was added in 5 mL of THF and the solution was allowed to warm to room temperature slowly. Saturated ammonium chloride solution and hexane were added and the organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated to a yellow oil. The oil was purified by flash chromatography (10% ethyl acetate–hexane) to give 8.91 g (77%) of product as a clear oil: IR (thin film) 1960, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.42 (t, 1, J = 3.5 Hz), 5.00 (quintet, 1, J = 6.6 Hz), 4.64 (d, t, 2, J = 6.6, 3.2 Hz), 4.09 (q, 2, J = 7.1 Hz), 3.54 (d, 2, J = 11.5 Hz), 3.44 (d, 2, J = 11.5 Hz), 2.99 (t, 1, J = 7.2 Hz), 2.36 (s, 2), 1.60–2.17 (m, 8), 1.20

(19) **General Methods.** Solvents were dried and/or distilled under a nitrogen atmosphere prior to use when this was deemed necessary from sodium benzophenone ketyl for ethyl ether, tetrahydrofuran (THF), and dimethoxyethane (DME), from CaH_2 for benzene, triethylamine, diisopropylamine, and hexamethylphosphoramide (HMPA), and from P_2O_5 for dichloromethane. Reagents were purified by standard procedures when appropriate.[20]

All reactions involving organometallic reagents were performed by using oven-dried glassware under nitrogen atmosphere. Most reactions were followed by analytical thin-layer chromatography with precoated Analtech Uniplates (0.25 μm thick). Compounds were visualized with ethanolic anisaldehyde spray, iodine vapor, or ethanolic phosphomolybdic acid spray. Column chromatography was done by using 70–230 mesh silica gel. Flash chromatography was performed by the method of Still.[21]

Capillary gas chromatographic analysis for monitoring irradiations and analyzing product mixtures was performed with Hewlett-Packard 5880A or 5790A instruments equipped with a series 5880A Level Four integrating recorder. A J&W Scientific Durabond-1 (a crosslinked polymethylsiloxane similar to SE-30) capillary column (L = 30 m, id = 0.25 mm, film thickness = 0.25 μm) was used in all cases.

Analytical samples were prepared by preparative gas–liquid partition chromatography (GLC) on Varian Aerograph A-90-P and 1420 instruments using a 2.5% SE-30 column on 60/80 Chromosorb W, 10 ft × 1/4 in.

Melting points were determined on a Büchi melting point apparatus and are uncorrected.

^{1}H NMR spectra were recorded on a UCB-250 (250 MHz, FT) and a UCB-200 (200 MHz, FT) spectrometer. ^{13}C NMR spectra were recorded on a UCB-250 (63 MHz) spectrometer. Chemical shifts are reported in units of δ from internal tetramethylsilane. ^{1}H NMR data are tabulated in the following order: Multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants in hertz. IR spectra were recorded on a Perkin-Elmer Model 281 spectrometer. Mass spectral data were collected on an AEI MS-12 (70 eV, low resolution), Finnigan 4000 (chemical ionization), or Kratos MS-50 (high resolution) instrument. Elemental analyses were performed by the Microanalytical Laboratory operated by the College of Chemistry, University of California, Berkeley.

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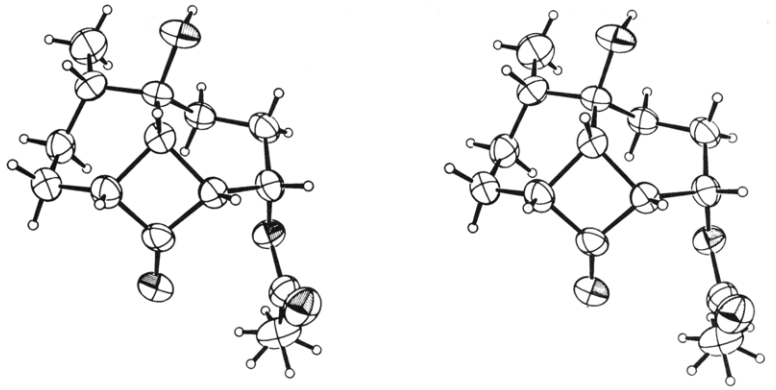

Figure 1. Stereoview of compound **24**.

(t, 3, J = 7.1 Hz), 1.00 (s, 3), 0.89 (s, 3). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.94; H, 9.08.

4-(1-Methyl-4,5-hexadienyl)cyclohex-3-enone 2,2-Dimethylpropanediyl Ketal (20). To a stirred suspension of lithium aluminum hydride (0.80 g, 20.0 mmol) in 50 mL of ether was added the ester **19** (10.0 g, 30.1 mmol) in 50 mL of ether at 0 °C. The mixture was allowed to warm to room temperature and was stirred for an additional h. A saturated sodium sulfate solution was added until the aluminum salts began to precipitate. The reaction mixture was filtered and the salts were washed with ethyl acetate. The solvent was removed with a rotary evaporator to yield 8.75 g of product as a clear viscous oil. Under a nitrogen atmosphere, the crude alcohol was dissolved in 100 mL of dry, distilled dichloromethane containing triethylamine (4.00 g, 40.0 mmol). Methanesulfonyl chloride (4.00 g, 35.0 mmol) was added at −78 °C and the solution was allowed to warm to −10 °C. Hexane (200 mL) was added and the solution was filtered, washed with saturated sodium bicarbonate solution, and dried ($MgSO_4$). The solution was concentrated to give 11.1 g of a yellow oil. The crude mesylate was dissolved in 80 mL of THF and lithium triethylborohydride (32.0 mL, 1.0 M THF solution, 32.0 mmol) was added at 0 °C with stirring. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. TLC analysis indicated the presence of starting material and an additional 5 mL of hydride solution was added. The reaction mixture was stirred overnight and TLC still evidenced a small amount of starting material. Ether–hexane solution (100 mL, 1:1, v/v) was added, followed by saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$), and concentrated to a colorless oil. The product was purified by flash chromatography (10% ethyl acetate–hexane) to give 5.45 g (66%) of a colorless oil: IR (thin film) 3060, 1955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (t, 1, 3.5 Hz), 4.97 (quintet, 1, J = 6.7 Hz), 4.57 (dt, 2, J = 6.7, 3.2 Hz), 3.50 (d, 2, 11.0 Hz), 3.45 (d, 2, J = 11.0 Hz), 2.27 (s, 2), 1.79–2.15 (m, 7), 1.30–1.40 (m, 2), 0.96 (s, 3), 0.92 (d, 3, J = 6.9 Hz), 0.84 s, 3). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.06; H, 10.27.

4-(1-Methyl-4,5-hexadienyl)cyclohex-3-enone (21). To a stirred solution of the ketal **20** (4.10 g, 14.8 mmol) in 110 mL of THF was added 45 mL of 1 N HCl. The solution was allowed to stir for 2 days, ether–hexane (150 mL, 1:1, v/v) was added, and the aqueous layer was separated. The organic phase was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated to a yellow oil. The residue was purified by flash chromatography (15% ethyl acetate–hexane) to give 2.36 g of product (83%) as a clear colorless oil: IR (thin film) 3060, 1955, 1720 cm^{-1}; ^1H NMR δ ($CDCl_3$) 5.42 (t, 1, J = 3.2 Hz), 5.03 (quintet, 1, J = 6.7 Hz), 4.60 (dt, 2, J = 6.7, 3.2 Hz), 2.81 (s, 2), 2.17–2.45 (m, 5), 1.83–1.95 (m, 2), 1.31–1.51 (m, 2), 0.98 (d, 3, J = 6.9 Hz); mass spectrum, exact mass calcd for $C_{13}H_{18}O$ m/e 190.1358 found m/e 190.1359.

4-Hydroxy-4-(1-methyl-4,5-hexadienyl)cyclohex-2-enone (11). To a rapidly stirred two-phase system containing the β,γ-unsaturated enone **20** (1.20 g, 6.24 mmol) in 35 mL of dichloromethane and 19 mL of 0.5 M aqueous sodium bicarbonate was added purified MCPBA (1.40 g, 8.11 mmol) at 0 °C. After 2 h, 75 mL of ether and 50 mL of saturated sodium bisulfite solution were added. The organic layer was separated, washed with 10% aqueous sodium hydroxide solution (3 × 30 mL), dried ($MgSO_4$), and concentrated to a clear oil. This oil was dissolved in 15 mL of methanol and, under nitrogen, was added to a stirred suspension of anhydrous potassium carbonate (140 mg, 1.00 mmol) in 20 mL of methanol at 0 °C. The mixture was stirred for 3 h, ether and saturated ammonium chloride solution were added, and the aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to a yellow oil. The oil was purified by flash chromatography (15–30% ethyl acetate–hexane gradient) to give 620 mg (48% from **21**) of product as a yellow oil: IR (thin film) 3440, 1955, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.68 (d, 1, J = 10.2 Hz), 5.89 (d, J = 10.2 Hz) and 5.88 (d, J = 10.2 Hz), sum of two previous bands = 1 H, 4.99–5.06 (m, 1), 4.58–4.64 (m, 2), 2.56–2.71 (m, 1), 2.29–2.39 (m, 2), 1.46–2.20 (m, 5), 1.10–1.27 (m, 2), 0.96 (d, J = 6.8 Hz) and 0.88 (d, J = 6.8 Hz), sum of two previous bands = 3 H; UV (methylcyclohexane) λ 210 (ϵ 4100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.45; H, 8.79.

(1*S,2*R**,5*S**,7*R**,11*R**)-1-Hydroxy-2-methyl-6-methylenetricyclo[5.3.1.0^{5,11}]undecan-8-one (22).** A solution of the diastereomeric enones **11** (900 mg, 4.37 mmol) in 650 mL of dry, distilled ether was placed in a Pyrex irradiation vessel (vacuum jacketed to allow water cooling for the lamp while the contents are at low temperature) and purged with nitrogen. The vessel was placed in an insulated cannister containing isopropyl alcohol which was maintained at −70 °C with a Cryocool. The solution was irradiated for 20 h with a 450-W Hanovia lamp fitted with a uranium glass filter. The solvent was evaporated and the crude oily product was purified by flash chromatography (15–30% ethyl acetate–hexane gradient) to give 520 mg of 75% pure product (capillary GC analysis). Spectral and analytical data were obtained on the pure fractions of product: IR (thin film) 3480, 3080, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.73–4.76 (m, 2), 3.64 (d, 1, J = 8.0 Hz), 3.29–3.41 (m, 1), 2.05–2.65 (m, 4), 1.40–1.82 (m, 7), 0.97 (d, 3, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 209.3, 148.9, 101.9, 71.2, 53.2, 42.7, 42.6, 40.4, 33.8, 27.3, 24.6, 22.6, 14.4; mass spectrum, exact mass calcd for $C_{13}H_{18}O_2$ m/e 206.1307, found m/e 206.1311.

(1*S,2*R**,5*S**,7*R**,8*R**,11*R**)-1-Hydroxy-2-methyl-6-methylene-8-acetoxytricyclo[5.3.1.0^{5,11}]undecane (23).** To a stirred solution of the partially purified photoproduct (520 mg, 75% pure, ca. 2.5 mmol) in 8 mL of THF was added L-Selectride (3.0 mL, 1.0 M, 3.0 mmol) at −78 °C, under nitrogen. The reaction mixture was stirred for 2 h, and ether and saturated ammonium chloride solution were added. The organic layer was separated, dried ($MgSO_4$), and concentrated to a clear oil. This oil, under nitrogen, was dissolved in 8 mL of dichloromethane containing triethylamine (1.50 g, 14.8 mmol) and 4-(dimethylamino)pyridine (60 mg, 0.5 mmol). Acetic anhydride (250 mg, 2.45 mmol) was added and the solution was stirred overnight. Ethyl acetate and saturated bicarbonate solution were added, the organic layer was separated, and dried ($MgSO_4$). The solution was concentrated and the oil was purified by flash chromatography to give 340 mg (31% from the mixture of enone diastereomers) of product as a white semisolid: IR (CCl_4) 3490, 3080, 1735, 1675 cm^{-1}; ^1H NMR δ 5.11 (m, 1), 4.96 (t, 1, J = 2.7 Hz), 4.62 (t, 1, J = 2.7 Hz), 3.33 (m, 1), 3.07 (m, 1), 2.02–2.17 (m, 3), 1.99 (s, 3), 1.23–1.85 (m, 8), 0.85 (d, 3, J = 6.0 Hz); ^{13}C NMR (CD_3OD) δ 172.5, 155.0, 102.3, 73.1, 70.9, 44.4, 43.3, 42.8, 41.2, 29.4, 24.32, 24.28, 22.6, 21.3, 15.0;

mass spectrum, exact mass calcd for $C_{15}H_{22}O_3$ m/e 250.1569, found m/e 250.1560.

(1S*,2R*,5S*,7S*,8R*,11R*)-1-Hydroxy-2-methyl-8-acetoxytricyclo[5.3.1.0^{5,11}]undecan-6-one (24). To a stirred solution of the acetate **23** (175 mg, 0.70 mmol) and trimethylamine *N*-oxide dihydrate (100 mg, 0.90 mmol) in 3 mL of THF/acetone/water (3:2:1, v/v/v) was added a small crystal of osmium tetraoxide under nitrogen. The solution was stirred for 12 h, ethyl acetate and solid sodium dithionite were added, and a black particulate suspension formed. The aqueous layer was separated, and the organic phase was filtered through anhydrous magnesium sulfate and concentrated to a clear viscous oil. This oil was dissolved in 3.5 mL of dry benzene, lead tetraacetate (350 mg, 0.79 mmol) was added, under nitrogen, and the mixture was stirred for 1 h. Ethyl acetate and saturated sodium bicarbonate solution were added. The organic layer was separated, filtered through anhydrous magnesium sulfate, and concentrated to afford 110 mg of crude product as colorless plates. The solid was recrystallized from ether–hexane to give 40 mg of pure product. The mother liquors were concentrated and the residue purified by flash chromatography to give an additional 47 mg of pure product as colorless plates (49% yield overall): mp 155–156 °C; IR ($CHCl_3$) 3590, 3500, 1770, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.05 (d, t, 1, J = 2.9, 8.3 Hz), 3.91 (d, t, 1, J = 2.6, 8.3), 3.43 (t, 1, J = 10.0 Hz), 2.36 (t, 1, J = 10.0 Hz), 2.09 (s, 3), 1.95–2.21 (m, 2), 1.24–1.80 (m, 8), 0.96 (d, 3, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 207.2, 171.3, 71.0, 67.9, 56.4 (overlapping resonances), 40.4, 35.7, 27.8, 23.1, 22.8, 21.0, 19.6, 14.4; mass spectrum (CI), M + 1, 253.

(1R*,2R*,5S*,7S*,11R*)-2-Methyl-8-acetoxytricyclo[5.3.1.0^{5,11}]undecan-6-one (27). To a stirred solution of cyclobutanone **24** (40 mg, 0.16 mmol), 4-(dimethylamino)pyridine (70 mg, 0.60 mmol), and triethylamine (100 mg, 1.0 mmol) in 2 mL of dry distilled dichloromethane was added distilled phosphorus oxychloride (80 mg, 0.52 mmol) at 0 °C under nitrogen. The solution became faintly purple colored and was allowed to warm to room temperature. Ethyl acetate and saturated sodium bicarbonate solution were added and the organic layer was separated. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to afford a crystalline material. This material was dissolved in 3.5 mL of ethyl acetate with 5 mg of 10% palladium-on-alumina under an atmosphere of hydrogen. The solution was stirred for one day, purged with nitrogen, and filtered through Celite. The filtrate was concentrated to give a white crystalline material which was purified by flash chromatography to yield 36 mg (95% overall) of product as white needles: mp 95–97 °C; IR ($CHCl_3$) 1780, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.97 (t, 1, J = 8.0 Hz), 3.86 (dt, 1, J = 2.3, 9.4 Hz), 3.13 (t, 1, J = 9.4 Hz), 2.57 (q, 1, J = 9.4 Hz), 2.09 (s, 3), 1.15–2.05 (m, 10), 0.92 (d, 3, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 208.4, 171.3, 69.0, 55.8, 53.0, 37.8, 32.3, 29.2, 26.5, 24.1, 20.9, 20.4, 19.8, 16.5; mass spectrum, exact mass calcd for $C_{14}H_{20}O_3$ m/e 236.1413, found m/e 236.1412.

Acknowledgment. This research was supported by Grant No. GM 27320, National Institute of General Medical Sciences, U. S. Public Health Service. The authors also wish to express their thanks to Molecular Design Limited for a generous donation of computer time and for providing access to the use of their ORTEP and DISP programs.

Registry No. (±)-**1** (Y′ = OH; R = CH_2OH), 91949-72-3; (±)-**11** (isomer 1), 91949-73-4; (±)-**11** (isomer 2), 91949-74-5; **14**, 30332-99-1; **15**, 5557-87-9; **16**, 32442-48-1; **17**, 69225-59-8; **18**, 69519-94-4; (±)-**19**, 91949-75-6; (±)-**20**, 91993-70-3; (±)-**21**, 91949-76-7; (±)-**22**, 91949-77-8; (±)-**23**, 91949-78-9; (±)-**24**, 91949-79-0; (±)-**25**, 91949-80-3; (±)-**26**, 91949-81-4; (±)-**27**, 91949-82-5; $(EtO)_2POCH_2CO_2Et$, 867-13-0; propargyl alcohol, 107-19-7; triethyl orthoacetate, 78-39-7.

Supplementary Material Available: Tables of atomic positional and thermal parameters (18 pages). Ordering information is given on any current masthead page.

Antineoplastic Agents. 104. Isolation and Structure of the *Phyllanthus acuminatus* Vahl (Euphorbiaceae) Glycosides[1a]

George R. Pettit,* Gordon M. Cragg, Matthew I. Suffness,[1b] Devens Gust, Fred E. Boettner,[1c] M. Williams,[1c] J. A. Saenz-Renauld,[1d] Peter Brown,[1e] Jean M. Schmidt, and Paul D. Ellis[1f]

Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, Arizona 85287

Received March 22, 1984

Three new antineoplastic glycosides, phyllanthostatins 1 (**2a**), 2 (**2c**), and 3 (**3a**), as well as phyllanthoside (**2b**), have been isolated from the Central American tree *Phyllanthus acuminatus* Vahl. The phyllanthostatins 1 (**2a**), 2 (**2c**), and 3 (**3a**) and phyllanthoside (**2b**) structures were completely assigned by detailed analyses of spectral data (principally by 400-MHz NMR) and have been confirmed by X-ray crystallographic analyses of degradation products. In addition to inhibiting growth of the murine P388 lymphocytic leukemia, both phyllanthostatin 1 and phyllanthoside were found to markedly retard progression of the murine B16 melanoma. One of these unique glycosides, phyllanthoside (**2b**), is in preclinical development at the U.S. National Cancer Institute.

The age-adjusted incidence of melanoma among Caucasians in North America has been increasing[2] and in areas (Texas[2] and Arizona[3]) of the American Southwest has reached an alarming rate.[4] Discovery of new drugs to improve melanoma treatment is an important objective of

(1) (a) For the 103rd part of this series, see: Pettit, G. R.; Goswami, A.; Cragg, G. M.; Schmidt, J. M.; Zou, J.-C. *J. Nat. Prod.*, in press. (b) Natural Products Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD 20014. (c) Polysciences, Inc., Paul Valley Industrial Park, Warrington, PA 18976. (d) School of Science, University of Costa Rica, San Jose, Costa Rica. (e) Deceased March 25, 1981. (f) Department of Chemistry, University of South Carolina, Columbia, SC 29208.

(2) Scotto, J.; Fears, T. "Cancer Epidemiology in the USA and USSR"; Levin, D. L., Blokhin, N. N., Eds.; NIH Publication No. 80-2044, 1980; p 129.

(3) Private communication, Alberts, D. S. Cancer Center, University of Arizona, Tucson, AZ.

(4) Even with stage 1 melanoma the five-year survival rate can fall to <50% in males with a primary neoplasm thicker than 2 mm (over 4 mm for females[5]). Treatment of human malignant melanoma with combinations of the plant biosynthetic products vincristine, vinblastine, and bleomycin with synthetic agents such as procarbazide has provided overwhelming evidence[6] that this disease will respond to cancer chemotherapy. But the general prognosis for malignant melanoma is still quite poor and the need is great for new and more effective cancer chemotherapeutic drugs.[7]

(5) Veronesi, U.; Cascinelli, N.; Morabito, A.; Bufalino, R.; van der Esch, E. P.; Preda, F.; Vaglini, M.; Rovini, D.; Orefice, S. *Int. J. Cancer* **1980**, *26*, 733–739.

0022-3263/84/1949-4258$01.50/0