ml each of ice-cold 4% hydrochloric acid, water, and 5% sodium bicarbonate, dried with magnesium sulfate, and evaporated to give 1.27 g (58%, based on amine) of colorless oil; λ_{max} 244 mμ (ε 13,600); $\nu_{max}^{CHCl_3}$ 2950, 1685 (s), 1640, 1464, 1442, 1386, 1100, 1083, and 896 cm^{-1} (Perkin-Elmer 137); $[\alpha]D$ −132° (*c* 1.13). The ketone could be distilled at 90–100° (bath temperature) (0.1 mm), but the distillate gave unsatisfactory analytical results.

Epicyclocolorenone (22). One milliliter of acetic acid containing unsaturated ketone **20** (162 mg, 0.74 mmole) was frozen at −10° and treated with 1.0 ml of a solution of hydrogen bromide (89 mg, 1.1 mmoles) in acetic acid. The mixture was placed in a water bath at 20° and agitated frequently until the solvent melted. After an additional 15 min at 20° it was diluted with 20 ml of water, and two 10-ml portions of hexane was used to extract the product. The hexane solution was washed with 5 ml of 5% sodium bicarbonate and 5 ml of water, dried with magnesium sulfate, and freed of solvent to leave 180 mg (81%) of clear oil which had λ_{max} 240 mμ (ε 16,000); $\nu_{max}^{CCl_4}$ 1698, 1635, and 750 cm^{-1} (Perkin-Elmer 137).

A. Commercial sodamide (600 mg, 15 mmoles) under 20 ml of 1,2-dimethoxyethane was decomposed by the addition of 5 drops of water. When evolution of ammonia ceased, the bromo ketone (1500 mg, 5 mmoles) in 10 ml of 1,2-dimethoxyethane was added. After 2 hr at reflux and concentration to 10 ml, the mixture was acidified with 100 ml of 3% boric acid and extracted with two 25-ml portions of hexane. The extract was washed with water and dried with magnesium sulfate to give 1300 mg of crude product, which was filtered through 15 g of Florisil in 200 ml of 25% chloroform–hexane and crystallized from pentane using Dry Ice to give 296 mg of semisolid that was chromatographed on 5 g of Woelm alumina (activity I), from which 150 ml of 15% chloroform–hexane eluted an oil that crystallized from pentane at Dry Ice temperature to give 97 mg of epicyclocolorenone, mp 64–69°. Sublimation at 0.17 mm (62°) gave 85 mg, mp 69–70°, undepressed on admixture with the product from method C; λ_{max} 253 mμ (ε 9300), $[\alpha]D$ −167° (*c* 1.03) (lit.[16] mp 68–68.5°; λ_{max}^{EtOH} 253 mμ (ε 15,154); $[\alpha]D^{20}$ −198° (*c* 6.9, $CHCl_3$)); $\nu_{max}^{CCl_4}$ 2908, 2850, 1696 (s), 1628, 1520, 1462, 1380, 1333, 1295, and 1075 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.51; H, 10.20.

B. The hydrobromide (182 mg) was refluxed for 2 hr under nitrogen with 10% potassium hydroxide in methanol (2 ml). Addition of water and isolation with ether gave a crude product (120 mg) which was chromatographed in hexane on active alumina (Woelm, basic, activity I, 4 g). Elution with hexane gave a number of fractions which crystallized spontaneously (total 30 mg). Sublimation at 60° (0.1 mm) and crystallization from pentane at −40° gave epicyclocolorenone (**22**), mp 65.5–67.5°.

C. Cyclocolorenone (**21**) which had the following constants: $[\alpha]D$ −446 ± 2° (*c* 1.91, $CHCl_3$); λ_{max} 262 mμ (ε 16,200); $\nu_{max}^{CCl_4}$ 2913, 1693 (s), 1624, 1460, 1415, 1387, 1380, 1338, 1307, 1119, and 1065 cm^{-1}; δ (CCl_4) 0.67–2.70 (9 H, diffuse), 0.78 (3 H, doublet, J = 7 cps), 1.04 (3 H), 1.23 (3 H), 1.65 (3 H, doublet, J = 2 cps), and 2.92 (1 H, diffuse), (328 mg), was chromatographed in pentane solution on 9 g of Woelm neutral alumina (activity I). The products were eluted with hexane–methylene chloride mixtures. Epicyclocolorenone (194 mg, 59%) was eluted first, crystallizing spontaneously, followed by four fractions (110 mg) whose infrared spectra showed a hydroxyl band with increasing intensity. The epicyclocolorenone had the same melting point, mixture melting point, and infrared spectrum as the product prepared by methods A and B. It also had $[\alpha]D$ −162 ± 1.5° (*c* 1.03, $CHCl_3$), and δ (CCl_4) 0.68–2.73 (10 H, diffuse), 1.02 (6 H), 1.22 (3 H), and 1.63 (3 H, triplet, J = 1.2 cps).

Acknowledgments. The authors are grateful to the National Science Foundation and to Firmenich et Cie, Geneva, for financial support. Rotatory dispersion curves were kindly measured by Professor W. Klyne, London, and Professor R. E. Corbett provided us with a generous sample of cyclocolorenone.

Synthetic Studies Leading to *dl*-Telekin and *dl*-Alantolactone

James A. Marshall, Noal Cohen, and Alan R. Hochstetler

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received February 10, 1966*

Abstract: Stereoselective total syntheses of *dl*-telekin (**25**) and *dl*-alantolactone (**33**), two lactone bitter principles of the eudesmane class of sesquiterpenes, are reported. Both syntheses employ the unsaturated lactone **13** as a key intermediate. This lactone was prepared from Hagemann's ester (**1**) by a sequence involving alkylation with 4-bromo-1-butene, hydrolysis and decarboxylation of the resulting monoalkylated product **2**, and addition of methyllithium to the dienone **3** thereby obtained. Formolysis of the resulting dienol **5** and hydrolysis and oxidation of the formic ester **6** thus secured gave octalone **8** which underwent alkylation with ethyl bromoacetate *via* the enamine **9b**. The keto ester **12**, prepared from the crystalline keto acid **11** obtained from the crude keto ester **10**, gave the desired lactone **13** upon treatment with methanolic potassium borohydride. The synthesis of *dl*-telekin involved photooxygenation of unsaturated lactone **13** to give principally hydroperoxide **19** which yielded the corresponding alcohol **20** upon reduction with potassium iodide in acetic acid. The total synthesis was completed by a sequence involving carbomethoxylation of hydroxy lactone **20**, reduction of the enolate thereby obtained, and oxidation of the resulting triol **23** using activated manganese dioxide. The synthesis of *dl*-alantolactone (**33**) proceeded *via* catalytic hydrogenation of unsaturated hydroxy lactone **20** and dehydration of the dihydro compound **29** using thionyl chloride in anhydrous pyridine. Unsaturated lactone **30** was thus formed in high yield. The α-methylene grouping was introduced as above by carbomethoxylation followed by reduction with lithium aluminum hydride. The resulting diol **32**, upon treatment with a suspension of manganese dioxide in benzene, afforded *dl*-alantolactone (**33**). These steps are described in detail, and evidence is presented for the proposed structures of various intermediates and reaction by-products encountered in the synthetic schemes.

The number of known lactone bitter principles belonging to the eudesmane class of sesquiterpenes[1] has increased steadily over the past several years with the most recent discoveries being made by Herz and his collaborators.[2] The formulas shown below for telekin[3] and alantolactone,[4] two typical eudesmane

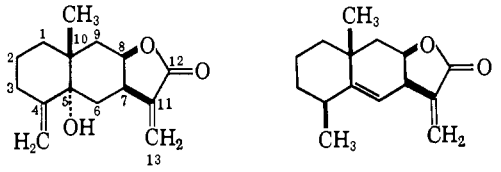
(1) For a recent review, see W. Cocker and T. B. H. McMurry, *Tetrahedron*, 8, 181 (1960).

(2) W. Herz, G. Högenauer, and A. Romo de Viar, *J. Org. Chem.*, **29**, 1700 (1964); W. Herz and N. Viswanathan, *ibid.*, **29**, 1022 (1964).

(3) V. Benešová, V. Herout, and W. Klyne, *Collection Czech. Chem. Commun.*, **27**, 498 (1962), and references therein.

(4) J. A. Marshall and N. Cohen, *J. Org. Chem.*, **29**, 3727 (1964), and references therein.

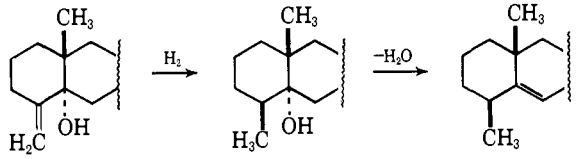
lactones, illustrate the characteristic arrangement of functionality and also depict the absolute stereochemistry at C-7, C-8, and C-10 in all currently known members of the group. The other members differ



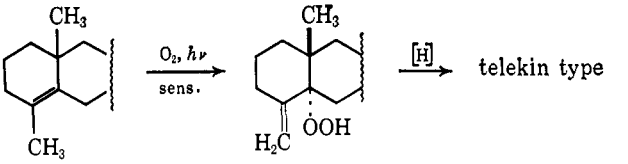
in the placement of hydroxy groups and the location of double bonds. Of the various substances belonging to this class, alantolactone seemed a likely target for synthetic studies. Because of its key role in correlating the other members, a stereoselective total synthesis of this substance would provide structural confirmation for most of the related natural products. Furthermore, a most interesting feature of alantolactone, the α-methylene-γ-butyrolactone grouping, commonly occurs among a wide variety of substances, including antibiotics,[5] hydroazulenic[6] and medium-ring[7] sesquiterpenes. This phase of the synthetic problem therefore held promise of widespread applicability to diverse types of important naturally occurring compounds.

Preliminary Considerations

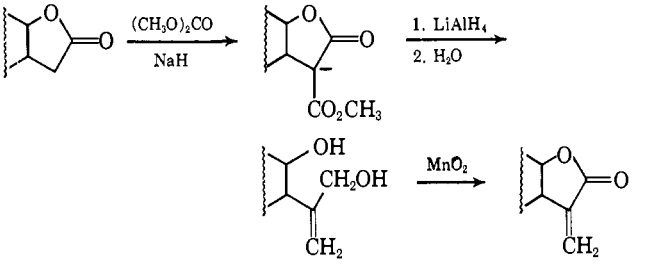
In considering various solutions to the synthetic problems presented by alantolactone, we favored one possibility whereby both alantolactone and telekin could be obtained by the same general route. This plan called for converting the 4-methylene-5α-hydroxy functionality characteristic of telekin to the 4β-methyl-5-ene functionality of alantolactone *via* hydrogenation and dehydration as shown below. With this in mind, we concentrated on telekin-like structures as initial synthetic goals. Of the routes which might be used to construct the requisite allylic alcohol system, photo-



sensitized oxygenation[8] of the appropriate tetrasubstituted olefin followed by reduction of the intermediate hydroperoxide, as depicted below, seemed a promising line of approach. In addition to the practical advantages of its directness, this scheme appeared particularly appealing from a theoretical standpoint because no information as to the selectivity of oxygenation reactions involving unsymmetrical tetrasubstituted olefins was available. Such an investigation therefore promised to uncover new facts of possible mechanistic importance in addition to providing a synthetic route to telekin-like structures.



In order to complete our plans for total syntheses of telekin and alantolactone, we required a reliable route to substituted α-methylene-γ-butyrolactones. Owing to its reactivity toward nucleophilic reagents[9] and a tendency to polymerize,[10] this functionality would ideally be introduced late in the sequence. A method was therefore needed which would prove compatible with groupings which might be present in prelactone intermediates. Some preliminary investigations with model compounds demonstrated the feasibility of converting substituted γ-butyrolactones to the corresponding α-methylene derivatives *via* carbomethoxylation, reduction of the resulting enolate with lithium aluminum hydride, and oxidation of the resulting diol with manganese dioxide.[11] A solution was thus available for both the functional and stereochemical aspects of the methylene lactone problem.



In view of the foregoing considerations, unsaturated lactone **13** commanded our attention as a key synthetic intermediate. This substance could, in principle, be prepared from unsaturated ketone **8** by a two-step sequence involving alkylation with ethyl bromoacetate and reduction[12] of the resulting keto ester. This route appeared particularly appealing as a result of the recent studies of Johnson and his collaborators,[13] which suggested a remarkably efficient route to the unsaturated ketone **8** through allylic cation-initiated cyclization of dienol **5**. Chart I presents these and related transformations leading to unsaturated lactone **13**.

Steps Leading to Lactone 13

The synthesis of lactone **13** commenced with ethyl 4-oxo-2-methyl-2-cyclohexenecarboxylate (**1**) (Hagemann's ester).[14] This material, upon alkylation with 4-bromo-1-butene,[15] afforded the 3-substituted deriva-

(5) C. J. Cavallito in "Medicinal Chemistry," Vol. I, C. M. Suter, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p 221.

(6) For a partial listing of the many representatives, see W. Herz, Abstracts of the Nineteenth National Organic Symposium of the American Chemical Society, Tempe, Ariz., June 13–17, 1965, pp 67–76.

(7) For recent discoveries, see T. R. Govindachari, B. S. Joshi, and V. N. Kamat, *Tetrahedron*, **21**, 1508 (1965); M. Suchy, V. Herout, F. Šorm, P. de Mayo, A. N. Starratt, and J. B. Stothers, *Tetrahedron Letters*, No. 51, 3907 (1964).

(8) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).

(9) *Cf.* J. W. Steele, J. B. Stenlake, and W. D. Williams, *J. Chem. Soc.*, 2627 (1959); G. H. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 1301 (1964); C. J. Cavallito, D. Fruehauf, and J. H. Bailey, *J. Am. Chem. Soc.*, **70**, 3724 (1948).

(10) *Cf.* E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 230 (1950).

(11) J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965). For a recently reported alternative synthesis of α-methylene-γ-butyrolactones, see H. Minato and I. Horibe, *Chem. Commun.* (London), 531 (1965).

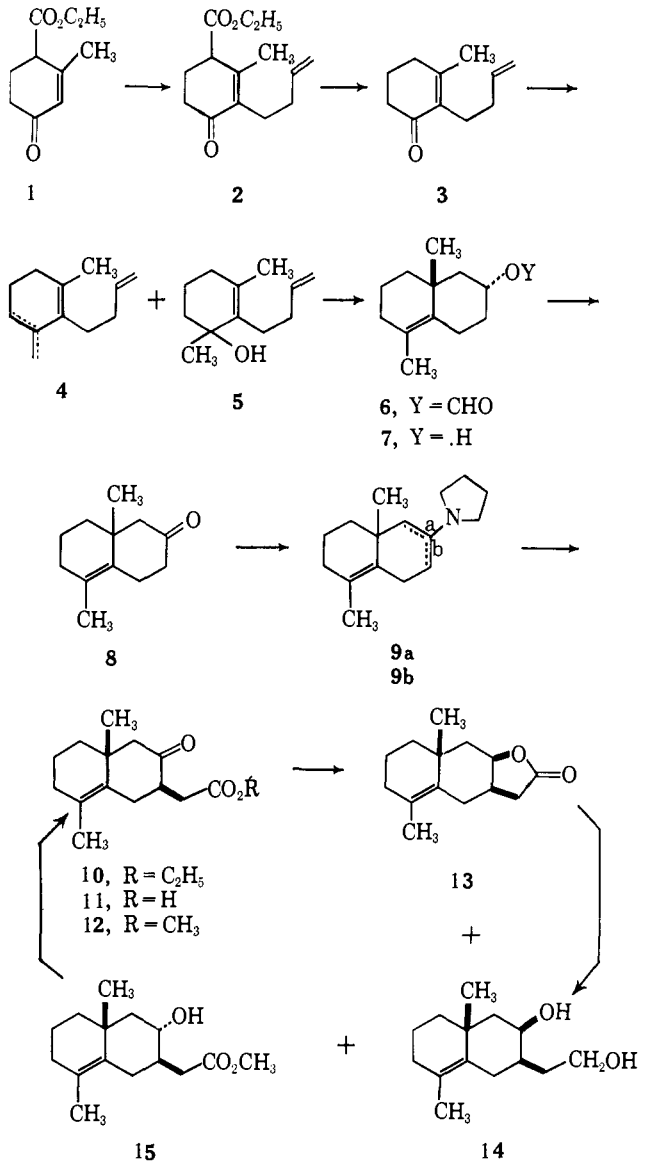
(12) *Cf.* the synthesis of 4-demethyltetrahydroalantolactone: J. A. Marshall, N. Cohen, and K. R. Arenson, *J. Org. Chem.*, **30**, 762 (1965).

(13) W. S. Johnson, W. H. Lunn, and K. Fitzi, *J. Am. Chem. Soc.*, **86**, 1972 (1964).

(14) L. I. Smith and G. F. Rouault, *J. Am. Chem. Soc.*, **65**, 631 (1943), and references cited therein.

(15) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1995 (1934).

Chart I



tive **2**. Previous studies[16] have shown that Hagemann's ester (**1**) undergoes alkylation at the 3 position in ethanolic sodium ethoxide. In fact, subsequent to our preparation of keto ester **2**, Johnson and co-workers[16c] described the synthesis of this substance using a modification of such an alkylation procedure.[16b] We were able to obtain the butenyl keto ester **2** in somewat better yield by conducting the alkylation in toluene or 1,2-dimethoxyethane using sodium hydride to prepare the enolate. The nmr spectrum of the resulting product (see the Experimental Section) confirmed our expectation that these conditions, like those previously reported,[16] would afford the 3-substituted derivative. The carboxylic salt, prepared *in situ* by heating keto ester **2** with ethanolic base, decarboxylated on prolonged heating to give dienone **3** in about 70% yield.

Initial attempts to obtain 1,3-dimethyl-2-(3-butenyl)-2-cyclohexen-1-ol (**5**) by treating dienone **3** with methylmagnesium bromide or iodide were not completely successful. Varying amounts of isomeric trienes resulted, sometimes to the exclusion of the expected alcohol **5**. We eventually discovered that aqueous ammonium chloride, used in the reaction work-ups (see the Experimental Section), caused the acid-sensitive allylic alcohol **5** to dehydrate. Meanwhile, by employing methyllithium and treating the reaction mixture with water to liberate alcohol **5** from its lithium salt, we were able to prevent this *in situ* dehydration reaction. Hydrolysis of the bromomagnesium salt (from dienone **3** and methylmagnesium bromide) likewise gave alcohol **5** in excellent yield when the ammonium chloride treatment was omitted from the work-up. Provided no acidic contaminants were present, this alcohol could be distilled, subjected to gas chromatography, and generally handled without difficulty. However, even traces of acidic materials caused its decomposition during distillation or gas chromatography. From a practical standpoint, the facile dehydration of alcohol **5** in no way jeopardized our proposed synthetic scheme, as both this alcohol and the corresponding mixture of olefin isomers **4** gave essentially the same mixture of bicyclic compounds when treated with anhydrous formic acid. Apparently, **4** and **5** lead to a common allylic cation[13] in formic acid. The major component of the resulting ester mixture may be regarded as formate **6** by analogy with the observations of Johnson and co-workers.[13] The crude product from this reaction, upon saponification with alcoholic base, afforded a mixture containing principally alcohol **7** (80% according to the gas chromatogram) which was oxidized by chromic acid reagent[17] to the corresponding ketone **8** (45% over-all yield from dienol **5**). The nmr spectrum of this olefinic ketone, in complete agreement with the assigned structure, showed peaks at 1.69 and 1.00 ppm resulting from the two types of methyl substituents. No absorption could be seen in the 5- to 7-ppm (vinyl H) region of the spectrum.

Ketone **8** smoothly yielded a pyrrolidine enamine derivative (**9**) by the method of Stork and co-workers.[18] The nmr spectrum of this substance displayed a broad band at 4.05 ppm due to the vinyl proton. Enamine **9a**, with an isolated vinyl proton, should show a relatively sharp peak in this region of its nmr spectrum. Although this peak might conceivably be broadened by allylic 1,3 coupling,[19] the width at half-height observed in the present case (10 cps) falls outside the range expected for such coupling and seems best accommodated by straightforward 1,2 coupling as in **9b**. We made no special search for the isomeric enamine **9a** and therefore cannot altogether exclude its formation from ketone **8**. However, the nmr spectrum of the crude enamine suggests the presence of no more than a minor amount of this isomer. Enamine **9b**, upon treatment with ethyl bromoacetate followed by hydrolysis of the reaction mixture and saponification of the resulting keto ester **10**, afforded the crystalline keto acid **11** in 77% yield. The high yield of C-alkylation product **10** constitutes additional evidence for the structure of enamine **9b** since steric factors should cause **9a** to undergo principally N-alkylation.[18] We know from earlier experi-

(16) (a) A. J. B. Edgar, S. H. Harper, and M. A. Kazi, *J. Chem. Soc.*, 1083 (1957); (b) R. A. Barnes and M. Sedlak, *J. Org. Chem.*, 27, 4562 (1962); (c) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Am. Chem. Soc.*, **87**, 5148 (1965).

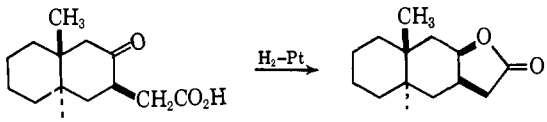
(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(18) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963)

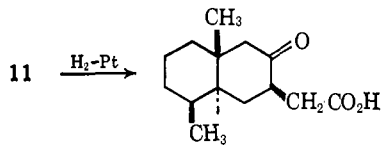
(19) T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *ibid.*, **85**, 1699 (1963); E. W. Garbisch, Jr., *ibid.*, **86**, 5561 (1964).

ence[12,20] that the conditions employed in saponifying keto ester **10** cause epimerization of the acetic side chain in similar keto esters and the stereochemistry of keto acid **11** is assigned accordingly.

In some previous work we prepared a prototype of lactone **13** *via* catalytic hydrogenation of the keto acid analog of **11** depicted below. This method proved

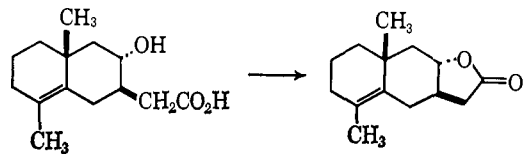


unsuccessful with unsaturated keto acid **11**. In this case keto acid **16** constituted the principal hydrogenation product.[21] We consequently found it necessary to use chemical means for reducing the keto group of



16

acid **11**. To this end, keto ester **12**, prepared from keto acid **11** using ethereal diazomethane, was treated with methanolic potassium borohydride, a reagent previously used for an analogous transformation in studies related to tetrahydroalantolactone.[22] The mixture of reduction products contained alcohol, lactone, and ester functionality according to the infrared spectrum and yielded three components, lactone **13** (74% yield), hydroxy ester **15** (14% yield), and diol **14** (11% yield), which could be separated by chromatography on silica gel. Lactone **13**, upon reduction with lithium aluminum hydride, afforded diol **14**, thereby establishing the relationship between these two components. Diol **14** was likewise obtained by treating lactone **13** with methanolic potassium borohydride, a transformation which undoubtedly represents the genesis of the former compound from keto ester **12**.[23] Hydroxy ester **15** gave the corresponding hydroxy acid

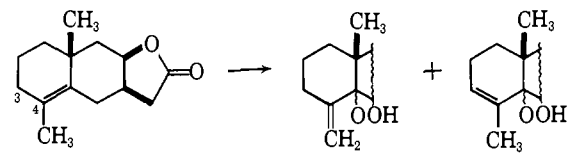


17 **18**

17 upon hydrolysis, and this material, when treated with *p*-toluenesulfonic acid in refluxing benzene, afforded lactone **18**. Apart from their differing appearances, lactone **18**, a crystalline substance, and lactone **13**, an oil, showed major differences in their infrared spectra. That these lactones differ only in configuration at the lactone ring oxygen was demonstrated through oxidation of hydroxy ester **15** under mild conditions to give keto ester **12**. Keto acid **11**, upon reduction with methanolic potassium borohydride, gave a mixture of hydroxy acids which could not be separated readily. The same difficulty was encountered with the mixture of lactones **13** and **18** obtained by treating the crude hydroxy acid mixture with *p*-toluenesulfonic acid in benzene. No attempts were made at selective lactonization.

Steps Leading from Lactone 13 to *dl*-Telekin (25)

Our choice of unsaturated lactone **13** as a key intermediate in the proposed sequence leading to telekin required that this substance undergo a stereoselective reaction with excited oxygen.[8,24] The most plausible oxygenation products of **13**, based on previous studies,[25] appear below. We could be reasonably certain that the *trans* products **19** and **27** would predominate over their *cis* counterparts **21** and **28** because of the steric hindrance exerted by the C-10 methyl group on the double bond of lactone **13**.[24a] However, the relative reactivity of the primary allylic hydrogens (C-4 CH_3 in **13**), leading to exocyclic olefinic hydroperoxides **19** and **21**, *vs.* the secondary C-3 allylic hydrogens, leading to endocyclic olefinic hydroperoxides **27** and **28**, could not be predicted with any assurance. With regard to our alantolactone synthetic scheme (Chart III), this point seemed inconsequential since both *trans* isomers **19** and **27** would undoubtedly furnish the same dihydro derivative (**29**) upon catalytic hydrogenation. Our plans for telekin (Chart II), on the other hand, demanded the exocyclic olefinic hydroperoxide **19** as a significant photooxygenation product of unsaturated lactone **13**.



13 **19**, *trans* **21**, *cis* **27**, *trans* **28**, *cis*

When unsaturated lactone **13** was treated with oxygen, according to the procedure of Nickon and Bagli[25b] using hematoporphyrin as a photosensitizer, two crystalline hydroperoxides could be isolated in over 70% yield. The major isomer (53%), mp 142–143.5°, was eluted from silica gel with 10% ether in benzene, and the minor isomer (22%), mp 150.5–152°, was isolated from the fractions eluted with 20 to 40% ether in benzene. Both isomers displayed bands at 6.07 and 11 μ in their infrared spectra and a pair of doublets in the 5- to 6-ppm region of their nmr spectra indicative of exocyclic methylene groupings. The lone C-8 hydrogen in each appeared at nearly the same chemical shift (*ca.* 4.8 ppm), but the splitting patterns differed markedly. In the spectrum of the major isomer this proton appeared as a quartet (J = 4 cps) which closely resembled the pattern seen for the equatorially oriented

(20) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.* 83, 606 (1961).

(21) Keto acid **16** was converted to tetrahydroalantolactone by the sequence previously reported for the 4-demethyl derivative;[12] see N. Cohen, Ph.D. Dissertation, Northwestern University, 1965. This conversion supports the stereochemistry assigned to keto acid **16**.

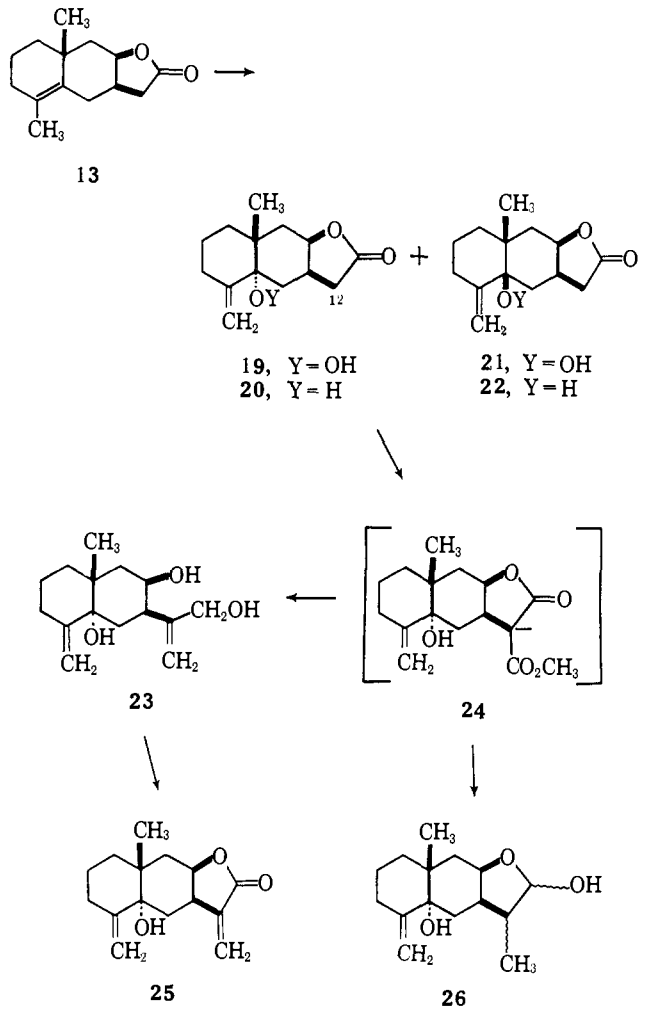
(22) W. Cocker, L. O. Hopkins, T. B. H. McMurry, and M. A. Nisbet, *J. Chem. Soc.*, 4721 (1961).

(23) For some examples wherein lactones are reduced by sodium borohydride, see N. W. Atwater, *J. Am. Chem. Soc.*, 83, 3071 (1961).

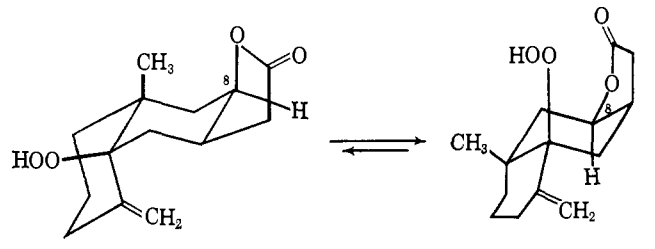
(24) (a) A. Nickon and W. L. Mendelson, *J. Org. Chem.*, 30, 2087 (1965), and previous papers; (b) C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Letters*, No. 46, 4111 (1965).

(25) (a) A. Nickon and W. L. Mendelson, *Can. J. Chem.*, 43, 1419 (1965); (b) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, 83, 1498 (1961); (c) G. O. Schenck, S. Schroeter, and G. Ohloff, *Chem. Ind.* (London), 459 (1962).

Chart II



H-8 in the nmr spectrum of the starting lactone **13**.[26] The minor isomer exhibited an nmr spectrum in which H-8 was seen as a complex pattern whose width at half-height suggested diaxial coupling.[26] The *trans* ring fusion of hydroperoxide **19** fixes its conformation and requires H-8 to be equatorial in the chair form, whereas for the *cis*-decalyl hydroperoxide **21**, conformational interconversion is possible (see below). Here nonbonded interactions appear least serious in the nonsteroid conformation wherein H-8 adopts an axial orientation and can thus exhibit diaxial coupling in the nmr spectrum. Therefore, the major and minor hydroperoxide isomers must be represented by **19** and **21**, respectively.



(26) For a previous application of this method to the determination of lactone stereochemistry, see W. Herz and L. Glick, *J. Org. Chem.*, 28, 2970 (1963).

The predominant hydroperoxide isomer (**19**) afforded the corresponding hydroxy lactone **20** upon treatment with potassium iodide in acetic acid. The infrared spectrum of this material confirmed the presence of the exocyclic methylene (6.1, 10.9 μ), alcohol (2.9 μ), and γ-butyrolactone (5.72 μ) groupings,[27] and the nmr spectrum displayed the expected peaks for exocyclic methylene and equatorial C-8 protons[26] in agreement with the proposed structure. The minor hydroperoxide (**21**) similarly afforded the analogous hydroxy lactone **22** whose infrared and nmr spectra furnished confirmatory structural evidence.

We were unable to isolate **27** or **28**, the hydroperoxides which would have resulted from participation by the secondary allylic hydrogens at C-3 of unsaturated lactone **13**. These compounds, if formed, represent at best minor (less than 25% yield) oxygenation products. Apparently, photochemically excited oxygen exhibits a marked preference for the methyl hydrogens of olefinic lactone **13**. After our initial observation of this phenomenon we carried out a detailed study of the oxygenation products from 1,10-dimethyl-1(9)-octalin, an olefin prototype of **13**. The results, which are reported elsewhere,[28] parallel those disclosed above for **13**. The preferred formation of the exocyclic olefin isomers (*e.g.*, **19** and **21**) can be attributed to the ability of a methyl hydrogen, by virtue of the relatively free rotation of the C–CH_3 bond, to easily attain the optimum alignment with the double bond for meeting the strict stereoelectronic requirement of the oxygenation reaction.[24a,29] Dreiding models indicate that similar alignment of the pseudo-axial hydrogen at C-3 requires some distortion of the cyclohexene ring and can be regarded as less favorable. In order for the pseudo-equatorial C-3 hydrogen to participate, the cyclohexene ring must adopt a boat conformation. This process represents the least favorable of the allowed possibilities.[25a,28,30]

Lactone **20** was treated with sodium hydride in dimethyl carbonate, and the intermediate lactone ester enolate thus formed[31] was reduced with lithium aluminum hydride after the dimethyl carbonate had been replaced with 1,2-dimethoxyethane. The resulting triol (**23**) was purified by column elution chromatography on Florisil. No attempt was made to characterize the by-products from this reduction which, on the basis of previous studies,[11] must consist principally of epimeric lactols (**26**). Triol **23** was smoothly oxidized by a stirred suspension of activated manganese

(27) *Cf.* K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, pp 24, 30, 44.

(28) J. A. Marshall and A. R. Hochstetler, *J. Org. Chem.*, 31, 1020 (1966).

(29) A straightforward steric argument has also been invoked recently to account for the preference shown by photochemically excited oxygen toward methyl hydrogens in certain trisubstituted olefins: E. Klein and W. Rojahn, *Tetrahedron*, 21, 2173 (1965).

(30) The allylic hydrogens at C-6 are not considered here because the definitive work of Nickon and co-wokers[24a] and our own previous findings[28] show that such hydrogens of analogous systems do not participate in this reaction. In the present case the axial C-8 lactone oxygen, by augmenting the hindrance of the C-6 axial hydrogen, should ensure the nonintervention of this hydrogen in the oxygenation of lactone 13.

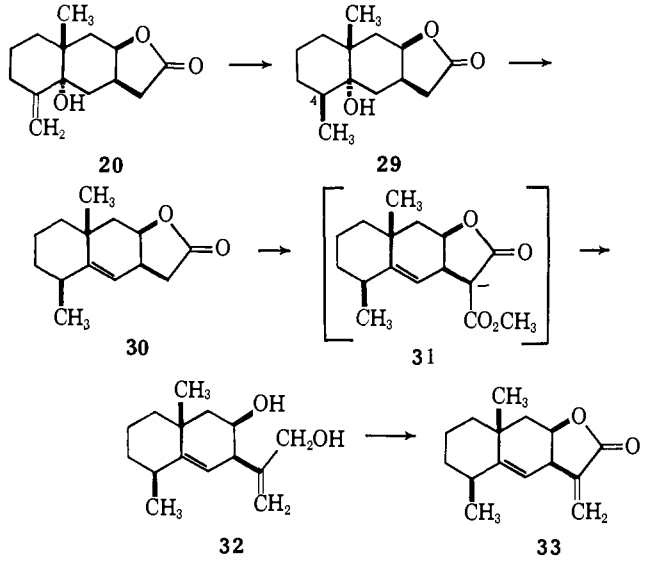
(31) Some of the dimethyl malonic enolate, derived from **24** by methanolysis, may also be formed as may the alkoxide resulting from reaction of the C-5 hydroxyl group of these intermediates with sodium hydride. However, all could give allylic alcohol **33** upon reduction with lithium aluminum hydride, and therefore no attempt was made to investigate the formation of these species: *cf.* J. A. Marshall and R. D. Carroll, *Tetrahedron Letters*, No. 47, 4223 (1965).

dioxide in benzene, and racemic telekin (**25**) was secured in crystalline form by evaporating the filtered reaction mixture. The infrared spectrum of this substance exactly matched the richly detailed published spectrum of the natural product.[32]

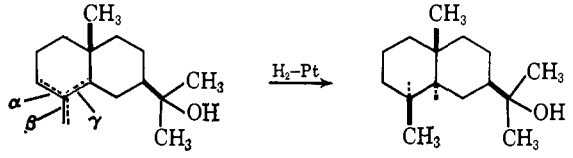
Steps Leading from Lactone 13 to *dl*-Alantolactone (33)

Chart III outlines the steps employed for the trans-

Chart III

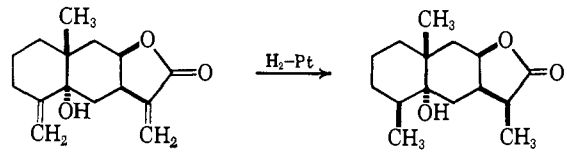


formation of lactone **20** to racemic alantolactone (**33**). The steric outcome of catalytic hydrogenation could be predicted with reasonable certainty for unsaturated hydroxy lactone **20** (**20** → **29**) by analogy with reported observations. For example, the isomeric eudesmols give a single dihydroeudesmol upon reduction over platinum.[33] Šorm and co-workers[32] report that telekin



α-, β-, and γ-eudesmol — dihydroeudesmol

affords essentially one tetrahydro derivative upon catalytic hydrogenation. Subsequent reactions suggest the steric course depicted below. An additional analogy which should be noted comes from our work on the oxygenation of 1,10-dimethyl-1(9)-octalin[28] where hydrogenation of the principal hydroperoxide product, *trans*-1-methylene-10-methyl-9-decalyl hydroperoxide (a prototype of telekin), yields *cis*-1,10-dimethyl-*trans*-9-decalol, a prototype of tetrahydrotelekin.



telekin — tetrahydrotelekin[34]

(32) V. Benešová, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **26**, 1350 (1961).
(33) F. J. McQuillin and J. D. Parrack, *J. Chem. Soc.*, 2973 (1956).
(34) Presumed stereochemistry: *cf.* W. Cocker and M. A. Nisbet, *ibid.*, 534 (1963), and ref 28.

Unsaturated lactone **20**, upon hydrogenation in acetic acid over Adams' catalyst,[32] afforded the dihydro derivative **29**, and this material, when treated with thionyl chloride in anhydrous pyridine, gave unsaturated lactone **30** in excellent over-all yield. The nmr spectrum confirmed the structure of **30** by showing a doublet at nearly the same chemical shift and with essentially the same coupling constant as the C-6 vinyl hydrogen of dihydroalantolactone.[4] The high degree of selectivity observed in the dehydration reaction supports the stereochemistry depicted for hydroxy lactone **29**. If special care was not exercised to ensure initially anhydrous dehydration conditions, some of the tetrasubstituted olefin **13** was formed, presumably *via* nonconcerted elimination pathways.[35]

The final remaining synthetic operation en route to *dl*-alantolactone followed the sequence outlined above for the synthesis of telekin (**25**) from 12-nortelekin (**20**). Thus, carbomethoxylation of lactone **30** gave the lactone ester enolate **31**[31] which, after treatment with lithium aluminum hydride in 1,2-dimethoxyethane, afforded diol **32**. As in the above case, we made no attempt to characterize the by-products from this reduction. Diol **32**, when treated with a suspension of activated manganese dioxide in benzene, afforded a crystalline compound identified as *dl*-alantolactone (**33**) by the exact identity of its infrared and nmr spectra with those of the natural product.[4] Thin layer chromatographic mobility and gas chromatographic retention time (peak enhancement) of the two materials were also identical.[36]

Experimental Section[37]

Melting points were determined on a Fisher-Johns hot stage. Nmr spectra were obtained with a Varian A-60 spectrometer. A Beckman IR-5 spectrophotometer was used for infrared spectra. Vpc analyses were performed on an F and M Model 720 instrument equipped with a thermal conductivity detector employing helium. Retention times are reported in minutes from the point of injection. The method of Bartlet and Smith[37d] was used to evaluate peak areas. Combustion analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

Ethyl 4-Oxo-2-methyl-3-(3-butenyl)-2-cyclohexenecarboxylate (2). A solution of 36.4 g of Hagemann's ester (**1**)[38] in 200 ml of toluene containing 9.6 g of 50% sodium hydride dispersed in mineral oil[39] was stirred at 110° until no more hydrogen was evolved (*ca.* 1 hr). The cooled reaction mixture was treated with 27 g of 4-bromo-1-butene[40] and stirred at reflux for 70 hr.[37a] The reaction mixture was chilled in an ice bath and 1.4 ml of acetic acid was cautiously added to decompose any excess sodium hydride, followed by 200 ml of water. The toluene layer was separated, the aqueous layer was extracted with ether, and the combined organic layers were dried,[37b] filtered, and concentrated under reduced pressure. The residue, upon distillation, yielded 30.0 g (64%) of butenyl keto ester **2**: bp 92–102° (0.2 mm); λ_{max}^{film} 3.25 (HC=C), 5.78 (ester CO), 6.0 (conjugated ketone CO), 6.12

(35) *Cf.* L. F. Fieser and J. Rigaudy, *J. Am. Chem. Soc.*, 73, 4660 (1951); S. G. Levine and M. E. Wall, *ibid.*, **82**, 3391 (1960).
(36) The work described in this paper has been reported in preliminary form: J. A. Marshall and N. Cohen, *ibid.*, 87, 2773 (1965); J. A. Marshall and A. R. Hochstetler, *Tetrahedron Letters*, No. 1, 55 (1966).
(37) (a) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere. (b) The organic extracts were dried over powdered anhydrous magnesium sulfate and filtered, with suction, through a sintered glass funnel. (c) The eudesmane numbering system is used for bicyclic and tricyclic intermediates. The prefixes "α" and "β" designate relative stereochemistry of racemic compounds. (d) J. C. Bartlett and D. M. Smith, *Can. J. Chem.*, 38, 2057 (1960).
(38) Supplied by Aldrich Chemical Co., Inc., Milwaukee, Wis.
(39) Alpha Inorganics, Inc., Beverly, Mass.
(40) Supplied by Columbia Organic Chemicals, Inc., Columbia, S. C.

(C=C), and 10.90 μ; $\delta_{TMS}^{CCl_4}$ 5.91–5.46 (CH_2=C*H*), 5.17–4.75 (C*H*$_2$=CH), 4.19 (CH_3CH_2O, quartet, J = 7.5 cps), 3.30 (*H*$CCO_2C_2H_5$, multiplet), 1.96 (CH_3C=C), and 1.25 ppm (CH_3CH_2O, triplet, J = 7.5 cps) (lit.[16c] bp 100–118° at 0.55–0.60 mm).

Comparable results were obtained when 1,2-dimethoxyethane was used as the solvent. Sodium ethoxide in ethanol gave the keto ester **2** in less than 40% yield.

3-Methyl-2-(3-butenyl)-2-cyclohexen-1-one (3). A 91.4-g sample of keto ester **2** was added to 235 ml of 15% ethanolic potassium hydroxide, and the mixture was heated to reflux for 24 hr.[37a] The ethanol was distilled at reduced pressure, the residue was treated with 600 ml of water, and the product was isolated by thorough extraction with ether. The extracts were washed with saturated brine, dried,[37b] and concentrated, and the residue was distilled through a 17 × 1 cm column packed with glass helices. The main fraction, bp 73.5–74.0° (0.7 mm), afforded 42.8 g (67.5%) of ketone: λ_{max}^{film} 5.99 (CO), 6.11 (C=CH_2), 7.22, and 10.94 μ; λ_{max}^{EtOH} 244 mμ (ϵ 12,250); $\delta_{TMS}^{CCl_4}$ 6.17–5.45 (CH_2=C*H*), 5.17–4.72 (C*H*$_2$=C), and 1.93 ppm (C-3 CH_3) [lit.[16c] bp 111–118° at 9–14 mm; λ_{max}^{EtOH} 243 mμ (ϵ 12,000)]. A gas chromatogram gave a major peak at 9.2 min (97.4%) and two smaller peaks at retention times of 4.9 (0.3%) and 10.8 min (2.3%).[41]

1,3-Dimethyl-2-(3-butenyl)-2-cyclohexen-1-ol (5). To an efficiently stirred solution containing 11 g of dienone **3** in 600 ml of anhydrous ether was added 150 ml of 5.2% ethereal methyllithium solution.[42] The mixture was stirred for 20 min after the addition and cautiously poured onto crushed ice. The ether layer was separated, and the aqueous phase was saturated with sodium chloride and thoroughly extracted with benzene. The combined extracts were washed with aqueous sodium thiosulfate and saturated brine, dried,[37b] and concentrated under reduced pressure. The residue was distilled affording 11.2 g (93%) of alcohol **4**, a colorless oil, bp 65–67° (0.05 mm): λ_{max}^{film} 2.95 (OH), 3.25 (HC=C), 6.08 (C=C), and 10.8–11.2 μ; $\delta_{TMS}^{CCl_4}$ 6.2–5.4 (CH_2=C*H*), 5.2–4.7 (C*H*$_2$=C), 2.78 (OH), 1.61 (CH_3C=C), and 1.22 ppm (CH_3COH).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.9; H, 11.2.

This material decomposed extensively on gas chromatography using the Carbowax column[41] at 120–150°, presumably owing to dehydration. With a 8 ft × 0.25 in. column of 1:4 KOH–Carbowax 20M on 60–80 Chromosorb W, gas chromatography could be carried out on this alcohol with no difficulty. With this column at 154° and a helium flow rate of 81 ml/min, alcohol **5** had a retention time of 9.9 min.

Substituting methylmagnesium bromide for methyllithium in the above experiment, we secured alcohol **5** in high yield. When this reaction mixture was treated with cold saturated aqueous ammonium chloride, material consisting largely of triene **4** was obtained: bp 70–80° (bath temperature) at 25 mm; λ_{max}^{film} 3.25 (HC=C), 6.09 (C=C), 6.22 (conjugated C=C), 10.02, 10.95, 11.40, and 12.63 μ; $\delta_{TMS}^{CCl_4}$ 4.57–6.22 (vinyl H) and 1.34–2.57 (aliphatic CH). The ratio (aliphatic H)/(vinyl H) = 3 could be estimated from the integrated spectrum. A gas chromatogram[43] indicated the exocyclic and endocyclic isomers of olefin **4** were formed in nearly equal amount (retention times of 2.7 and 2.9 min).

An ethereal solution of alcohol **5**, upon shaking with saturated aqueous ammonium chloride, was converted to a mixture containing principally the trienes **4** as revealed by the infrared spectral changes.

4,10-Dimethyl-4-octal-8-one (8).[37c] An 11-g sample of alcohol **5** was added to 600 ml of anhydrous formic acid[44] with rapid stirring.[37a] After 10 min, the solution was cautiously added with efficient stirring to a cold solution containing 700 g of sodium hydroxide in 700 ml of water.[45] The resulting mixture was thoroughly extracted with ether and the combined extracts were washed with saturated brine, dried,[37b] and concentrated.

The residue, which consisted largely of formic esters (λ_{max} 5.76 μ), was dissolved in 220 ml of 15% ethanolic potassium hydroxide and allowed to stand at room temperature for 13 hr.[37a] Most of the ethanol was removed under reduced pressure, saturated brine was added to the residue, and the mixture was thoroughly extracted with ether. The combined extracts were dried[37b] and concentrated under reduced pressure giving 10.6 g of material which consisted largely of alcohol **7**: λ_{max}^{film} 3.00 (OH), 7.27, and 9.3–9.8 μ. The gas chromatogram[46] of a distilled sample, bp 65–73° (0.06 mm), from a typical run showed peaks at 74.5 (4.6%), 124.5 (7.4%), 161.5 (78.8%), and 213 cm (9.2%).

Comparable results were obtained from cyclization experiments in which the concentration of dienol **5** in formic acid ranged from 0.02 to 0.5 *M*. The isomeric trienes **4** gave essentially the same product mixture as the dienol **5** upon dissolution in formic acid.

A 19.6-g sample of crude octalol **7**, similar in quality to the material described above, was dissolved in 835 ml of reagent grade acetone, and the solution was maintained at 0–10° while 32 ml of chromic acid reagent[17] was added dropwise over 30 min. Isopropyl alcohol was added to destroy the excess oxidizing agent, and the mixture was treated with water to dissolve the salts and saturated with sodium chloride. The organic layer was separated and the aqueous phase was thoroughly extracted with ether. The combined organic solutions were washed with saturated aqueous sodium bicarbonate and saturated brine, dried,[37b] and concentrated under reduced pressure. The residue was distilled giving 10.5 g (53%) of octalone **8**: bp 70° (0.2 mm); λ_{max}^{film} 5.83 (CO), 7.72, 8.08, 8.29, 9.06, 10.25, 11.59, and 11.75 μ; $\delta_{TMS}^{CCl_4}$ 1.69 (C-4 CH_3) and 1.00 ppm (C-10 CH_3).

A gas chromatogram[47] showed peaks at 4.1 (92%) and 5.4 min (8%).

The 2,4-dinitrophenylhydrazone derivative exhibited mp 197–199°, after three recrystallizations from ethanol–ethyl acetate.

Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 60.31; H, 6.20; N, 15.63. Found: C, 60.2; H, 6.2; N, 15.7.

(4,10β-Dimethyl-8-oxo-4-octal-7β-yl)acetic Acid (11).[37c] The method of Stork and co-workers[18] is described. A solution containing 8.43 g of octalone **8** and 13.5 g of pyrrolidine in 200 ml of dry benzene was stirred at reflux for 19 hr, with removal of water *via* a Dean–Stark trap.[37a] The solvent was removed under reduced pressure and the residue [λ_{max}^{film} 6.08 μ (C=C); $\delta_{TMS}^{CCl_4}$ 4.05 (H-7, width at half-height = 10 cps), 1.57 (C-4 CH_3), and 1.06 ppm C-10 CH_3)] was used without purification.

This material was dissolved in 200 ml of dry benzene, and 12 g of ethyl bromoacetate was added in one portion.[37a] After 20.5 hr at reflux, the mixture was treated with 45 ml of water containing a few drops of acetic acid, and the reflux period was extended for 1.5 hr. The cooled mixture was washed with 10% aqueous hydrochloric acid, the combined aqueous washes were extracted with ether, and the combined organic solutions were dried,[37b] filtered, and concentrated under reduced pressure.

The residue was treated with 100 ml of 10% ethanolic potassium hydroxide at room temperature for 13 hr.[37a] Most of the ethanol was removed under reduced pressure, the residue was dissolved in 600 ml of water, and the aqueous solution was washed three times with ether. The acidic material was liberated from the aqueous phase by acidification using cold 10% aqueous hydrochloric acid and the aqueous mixture was thoroughly extracted with benzene. The combined extracts were washed with saturated brine solution, dried,[37b] and concentrated under reduced pressure giving 8.67 g (77.4%) of crystalline acid. Recrystallization from hexane–benzene afforded 5.56 g of solid, mp 128–130°, and 0.31 g, mp 125–129°, as the second crop. A sample of the first crop material, after three recrystallizations from hexane–benzene, exhibited mp 129.5–130.5°, $\lambda_{max}^{CHCl_3}$ 2.8–4.2 (acid OH) and 5.87 μ (CO).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.14; H, 8.55. Found: C, 71.3; H, 8.6.

Methyl (4,10β-Dimethyl-8-oxo-7β-yl)acetate (12).[37c] A solution of 2.36 g of keto acid **11** in 50 ml of anhydrous ether was treated with ethereal diazomethane until the yellow color of the added reagent was no longer discharged. After 5 min, sufficient acetic

(41) A 13 ft × 0.25 in. 16% Carbowax 20M on 60–80 Diatoport S column was employed at a temperature of 188° and a helium flow rate of 83 ml/min.

(42) Foote Mineral Co., Exton, Pa.

(43) The 8 ft × 0.25 in. KOH–Carbowax column described above was employed at 154° with a flow rate of 81 ml/min.

(44) Commercial anhydrous formic acid could be used directly with excellent results.

(45) An alternative procedure which obviates this neutralization step consists of diluting the formic acid solution with an equal volume of water and extracting with hexane. This procedure, which was developed by Myron T. Pike of our laboratory, gave excellent results in a large-scale cyclization reaction using the crude alcohol obtained from dienone **3** and methyllithium. Because the formate **6** forms an azeotrope with formic acid, the cyclization reaction mixture could not be directly concentrated by distilling the formic acid without some loss (*ca.* 15%) of material.

(46) A 7.5 ft by 1/8 in. column packed with Craig succinate on 60–80 Chromosorb W was used at 180° with a nitrogen carrier gas pressure of 12 psi. Analyses were performed by Pedro J. Neustaedter at Stanford University.

(47) The Carbowax column[41] was used at 180° with a helium flow rate of 140 ml/min.

acid was added to restore the solution to a colorless state, the solvent was removed under reduced pressure, and the residue was distilled affording 2.39 g (95.6%) of keto ester **12**: bp 110–120° (bath temperature) at 0.07 mm; λ_{max}^{film} 5.77 (ester CO), 5.85 (ketone CO), 9.54, 10.00, and 11.30 μ; $\delta_{TMS}^{CCl_4}$ 3.66 (CH_3O), 1.74 (C-4 CH_3), and 1.02 ppm (C-10 CH_3).

The 2,4-dinitrophenylhydrazone derivative exhibited mp 163.5–165° after several recrystallizations from methanol–chloroform.

Anal. Calcd for $C_{21}H_{26}N_4O_6$: C, 58.58; H, 6.10; N, 13.02. Found: C, 58.6; H, 6.1; N, 12.8.

(4,10β-Dimethyl-8β-hydroxy-4-octal-7β-yl)acetic Acid Lactone (13)[37c] A cooled solution of 7.43 g of keto ester **12** in 300 ml of absolute methanol was treated with 2.28 g of potassium borohydride and stirred at 0° for 0.5 hr and at room temperature for an additional 5.5 hr. The excess borohydride was decomposed with acetone and the solution was concentrated under reduced pressure. The residue was treated with water and thoroughly extracted with ether. The combined organic extracts were washed with saturated brine, dried,[37b] and concentrated under reduced pressure, and the oily residue was chromatographed on 500 ml of silica gel. The fractions eluted with 5% ether in benzene afforded 4.85 g (74%) of lactone **13**: λ_{max}^{film} 5.63 (CO), 8.20, 8.52, 8.67, 10.49, and 10.90 μ; $\delta_{TMS}^{CCl_4}$ 4.56 (H-8 quartet, J = 5 cps), 1.66 (C-4 CH_3), and 1.13 ppm (C-10 CH_3). Short-path distillation at 90° (0.05 mm) afforded the analytical sample.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 76.0; H, 9.2.

2-(4,10β-Dimethyl-8β-hydroxy-4-octal-7β-yl)ethan-1-ol (14).[37c] The later ether chromatographic fractions, from the experiment described above in connection with the preparation of lactone **13**, afforded 0.71 g (10.7%) of crystalline diol **14**: mp 124–126°; λ_{max}^{KBr} 2.99 (OH), 7.39, 9.37, 9.57, and 9.83 μ. The analytical sample, mp 126–127°, was obtained after one recrystallization from heptane–ethyl acetate.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.7; H, 10.8.

This diol was found to be identical (melting point, infrared spectrum) with the diol obtained by reducing lactone **13** with lithium aluminum hydride in ether. Lactone **13**, upon treatment with methanolic potassium borohydride under the conditions described above, gave diol **14** in 13% yield.

Methyl (4,10β-Dimethyl-8α-hydroxy-4-octal-7β-yl)acetate (15).[37c] The early ether fractions, from the chromatography described above in connection with the preparation of lactone **13**, afforded 1.00 g (13.5%) of oily hydroxy ester **15**: bp 130–140° (bath temperature) at 0.04 mm; λ_{max}^{film} 2.92 (OH), 5.78 (CO), 8.68, and 9.54 μ.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.38; H, 9.60. Found: C, 71.6; H, 9.7.

This material, upon treatment with chromic acid reagent in acetone as described above for octalol **7**, gave the keto ester **12** (98% yield) identified through comparison of the infrared spectra.

(*trans*-4β,10β-Dimethyl-8-oxodecal-7β-yl)acetic Acid (16).[37c] A 500-mg sample of keto acid **11** in 75 ml of glacial acetic acid was shaken with 50 mg of platinum oxide in a Parr apparatus under an initial hydrogen pressure of 50 psi. After 17 hr, the mixture was filtered, the solvent was removed under reduced pressure, and the residue was dissolved in ether and thoroughly washed with aqueous sodium bicarbonate solution. The combined aqueous washes were acidified with dilute hydrochloric acid and thoroughly extracted with ether. The combined extracts were dried[37b] and concentrated under reduced pressure giving 406 mg (80.5%) of solid material. The analytical sample, after three recrystallizations from hexane–benzene, exhibited mp 134–135°; $\lambda_{max}^{CHCl_3}$ 2.8–4.2 (acid OH), 5.86 (CO), and 8.6 μ; $\delta_{max}^{CCl_4}$ 0.93 (C-4 CH_3 doublet, J = 6 cps) and 0.87 ppm (C-10 CH_3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.32. Found: C, 70.3; H, 9.4.

A mixture of this keto acid and the starting unsaturated keto acid **11** exhibited mp 107–120°. Keto acid **16** was recovered unchanged from refluxing benzene containing *p*-toluenesulfonic acid, thus indicating that the ketone carbonyl had not been hydrogenated. Keto acid **16** was also obtained as the principal product when the hydrogenation was conducted at atmospheric pressure.

(4,10β-Dimethyl-8α-hydroxy-4-octal-7β-yl)acetic Acid (17).[37c] A mixture of 304 mg of hydroxy ester **15** and 10 ml of 10% aqueous sodium hydroxide was heated to reflux with stirring for 3 hr.[37a] The cooled solution was washed with ether and acidified with dilute hydrochloric acid giving a solid which was collected by filtration, washed well with water, and air dried. In this manner, 226 mg (79%) of hydroxy acid **15** was obtained: mp 144–147°; λ_{max}^{Nujol} 2.97 (OH), 3.1–4.2 (acid OH), 5.90 (CO), 9.65, and 10.72 μ. After two recrystallizations from ethyl acetate, white prisms, mp 157–158°, were secured.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.32. Found: C, 70.5; H, 9.25.

(4,10β-Dimethyl-8α-hydroxy-4-octal-7β-yl)acetic Acid Lactone (18).[37c] A solution of 100 mg of hydroxy acid **17** and *ca.* 10 mg of *p*-toluenesulfonic acid was heated at reflux and stirred for 0.5 hr.[37a] A Dean–Stark trap was employed to collect the water formed in the reaction. After cooling, the benzene solution was washed with aqueous sodium bicarbonate and saturated brine, dried,[37b] and concentrated. The residue was crystallized from hexane giving 63 mg (68%) of white prisms: mp 80–82°; $\lambda_{max}^{CCl_4}$ 5.61 (CO), 8.25, 8.40, 8.54, 8.78, 9.12, 9.42, 9.51, 9.71, 10.03, 10.71, 11.08, 11.82, and 11.93 μ. This compound exhibited polymorphic behavior. One additional recrystallization from hexane gave prisms, mp 85–87°, and this material gave needles, mp 98–99°, after one more recrystallization from hexane. The infrared spectra of these samples showed no changes. The higher melting modification was used as the analytical sample.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 76.5; H, 9.2.

Photooxygenation of Lactone 13. (10β-Methyl-4-methylene-5α-hydroperoxy-8β-hydroxy-7β-decalyl)acetic Acid Lactone (19)[37c] **and (10β-Methyl-4-methylene-5β-hydroperoxy-8β-hydroxy-7β-decalyl)acetic Acid Lactone (21)**.[37c] The procedure of Nickon and Bagli[25b] was followed. A 30-mm Pyrex tube surrounded by three 15-w fluorescent lamps was charged with a solution of 3.48 g of lactone **13** and 202 mg of hematoporphyrin in 215 ml of anhydrous pyridine. Oxygen was admitted through a gas dispersion tube and the mixture was irradiated during 8 hr. The solution was diluted with ether, warmed briefly on a steam bath with decolorizing carbon, and filtered. Removal of solvent under reduced pressure afforded 4.13 g of crude hydroperoxide, which was immediately chromatographed on 500 ml of Florisil. The fractions eluted with 10% ether in benzene afforded 2.11 g (53%) of crystalline hydroperoxide **19**: mp 135–141°; λ_{max}^{KBr} 2.99 (OOH), 5.68 (CO), 6.07 (C=CH_2), 8.07, 8.15, 8.35, 8.57, 9.79, 10.41, 10.76, 11.10, and 11.56 μ; $\delta_{TMS}^{CHCl_3}$ 5.19, 4.89 (C=CH_2), 4.77 (H-8 quartet, J = 4 cps), and 1.02 ppm (C-10 CH_3). The analytical sample, obtained after two recrystallizations from heptane–ethyl acetate, exhibited mp 142–143.5°, and was sublimed at 130° (0.02 mm) prior to combustion analysis.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.7; H, 8.0.

The fractions eluted with 20 to 40% ether in benzene afforded 0.87 g (22%) of crystalline hydroperoxide **21**: mp 142–151°; λ_{max}^{KBr} 2.99 (OH), 5.72 (CO), 6.07 (C=CH_2), 8.17, 8.31, 8.51, 10.12; 10.28, 10.67, 10.93, and 11.47 μ; $\delta_{TMS}^{CHCl_3}$ 5.33, 5.18 (C=CH_2), 4.75 (H-8 multiplet, width at half-height = 20 cps), and 1.11 ppm (C-10 CH_3). Two recrystallizations from heptane–ethyl acetate afforded the analytical sample, mp 150.5–152°, which was sublimed at 120° (0.02 mm) prior to combustion analysis.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.6; H, 8.1.

The fractions eluted with acetone afforded 0.92 g of oily material displaying carbonyl absorption (5.85 μ) not present in the spectrum of the crude hydroperoxide mixture. The band at 5.7 μ, characteristic of the lactone carbonyl, was also present, indicating the material was related to the starting lactone **13**. Thus essentially all of the material is accounted for by lactones **19**, **21**, and this mixture of ketonic substances.

(10β-Methyl-4-methylene-5α,8β-dihydroxy-7β-decalyl)acetic Acid Lactone (20).[37c] To a 1.00-g sample of hydroperoxide **19** dissolved in 9 ml of ether and 11 ml of absolute methanol was added a solution of 2.66 g of potassium iodide in 17 ml of glacial acetic acid and 6 ml of water.[37a] The solution was stirred at room temperature for 4 hr, neutralized with excess saturated aqueous sodium bicarbonate, and extracted thoroughly with ether. The combined extracts were washed with saturated aqueous sodium thiosulfate solution and saturated brine, dried,[37b] and concentrated under reduced pressure. The residue was crystallized from heptane–ethyl acetate affording 737 mg (78.5%) of hydroxy lactone **20**: mp 158–159°; λ_{max}^{KBr} 2.90 (OH), 6.08 (C=CH_2), 5.72 (CO), 8.18, 8.43, 8.53, 9.42, 10.42, 10.93, and 11.53 μ; $\delta_{TMS}^{CHCl_3}$ 5.01, 4.85 (C=CH_2), 4.77 (H-8 quartet, J = 4 cps), 1.96 (OH), and 0.98 ppm (C-10 CH_3).

The analytical sample, mp 159–160°, was obtained after an additional recrystallization from heptane–ethyl acetate.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.2; H, 8.7.

A second crop afforded 101 mg (10.8%) of material, mp 155–158°, whose infrared spectrum was identical with that of the first crop.

The same product was also formed when hydroperoxide **19** was treated with ethanolic sodium borohydride. The material obtained by this procedure was contaminated with reduction products of the lactone grouping.

(10β-Methyl-4-methylene-5β,8β-dihydroxy-7β-decalyl)acetic Acid (7→8) Lactone (22).[37c] The reduction procedure previously outlined for hydroperoxide **19** was followed using 202 mg of hydroperoxide **21**. The product was isolated as above, and a yellow oil was obtained which solidified upon cooling. Recrystallization from heptane–ethyl acetate afforded 160 mg of yellow crystals, mp 106–116°. This material upon sublimation followed by two additional recrystallizations afforded 102 mg (54%) of white blades: mp 130–132°; λ_{max}^{KBr} 3.01 (OH), 6.09 (C=CH$_2$), 5.70 (CO), 8.34, 8.42, 8.54, 9.33, 9.90, 10.08, and 11.04 μ; $\delta_{TMS}^{CHCl_3}$ 5.14, 5.05 (C=CH$_2$), 4.85 (H-8 multiplet, width at half-height = 16 cps), 2.15 (OH), and 0.97 ppm (C-10 CH$_3$).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.2; H, 8.2.

2-(10β-Methyl-4-methylene-8β,5α-dihydroxy-7β-decalyl)-2-propen-1-ol (23).[37c] A 500-mg sample of hydroxy lactone **20**, dissolved in 20 ml of dimethyl carbonate, was added to 400 mg of a 50% sodium hydride–mineral oil dispersion which had been freed of the mineral oil under a positive nitrogen pressure by five washings with heptane. After refluxing for 5 hr,[37a] the mixture was cooled and the excess dimethyl carbonate was removed under reduced pressure. The residual solid enolate (**24**) was suspended in 30 ml of anhydrous 1,2-dimethoxyethane, 380 mg of lithium aluminum hydride was added, and the mixture was heated at reflux for 2 hr.[37a] Ether (10 ml) was added to the cooled mixture which was then stirred at room temperature for an additional 10 hr, treated with 20 ml of ether and 1.9 ml of water, stirred for 4 hr, and filtered. The solvent was removed under reduced pressure affording 510 mg of solid which was chromatographed on 60 ml of Florisil. The early 20% ether in benzene fractions afforded 32 mg of material, mp 180–188°, after recrystallization from heptane–ethyl acetate: λ_{max}^{KBr} 2.91, 3.00 (OH), 6.09 (C=CH$_2$), 9.73, 10.31, and 11.16 μ. This material is presumably one of the isomeric lactols (**26**) and was investigated no further.

The fractions eluted with 40–50% ether in benzene afforded 287 mg of crystalline material. Recrystallization from heptane–ethyl acetate gave 161 mg (32%) of triol **23**: mp 136.5–139.5°; λ_{max}^{KBr} 2.95 (OH), 6.09 (C=CH$_2$), 9.67, 9.98, 10.15, and 10.94 μ; δ_{max}^{DMSO} 5.10, 5.00, 4.81 (C=CH$_2$), and 1.05 ppm (C-10 CH$_3$). Two additional recrystallizations from the same solvent pair afforded the analytical sample, mp 139.5–141.5°, which was sublimed at 110° (0.02 mm) prior to combustion analysis.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.58. Found: C, 71.1; H, 9.8.

***dl*-Telekin (25).** A mixture of 102 mg of triol **23** and 1.40 g of activated manganese dioxide[48] in 10 ml of anhydrous benzene was stirred at room temperature for 6.5 hr. The mixture was filtered and the solvent was removed under reduced pressure affording 83 mg (83%) of white crystals: mp 194.5–196°; $\lambda_{max}^{CHCl_3}$ 2.80–2.95 (OH), 5.70 (CO), 6.00, 6.08 (C=CH$_2$), 7.91, 8.52, 8.76, 9.00, 9.98, 10.24, 10.38, 10.54, 11.00, and 11.52 μ; $\delta_{TMS}^{CHCl_3}$ 6.27, 5.71 (C-11 CH$_2$ doublet, J = 1.5 cps); 4.98, 4.80 (C-4 CH$_2$ triplet, J = 1.5 cps), 4.65 (H-8 multiplet), and 0.98 ppm (C-10 CH$_3$). The infrared spectrum was identical with the published spectrum of natural telekin.[32] This material, upon recrystallization from heptane–ethyl acetate followed by sublimation at 120° (0.15 mm), afforded the analytical sample, mp 195–196.5°.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.5; H, 8.0.

(4β,10β-Dimethyl-5α,8β-dihydroxy-7β-yl)acetic Acid Lactone (29).[37c] A 60-mg sample of unsaturated hydroxy lactone **20** in 10 ml of acetic acid was stirred with platinum (from 50 mg of platinum oxide) in a hydrogen atmosphere for 0.5 hr. Slightly less than the theoretical quantity of hydrogen was absorbed. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from benzene giving 45 mg (74%) of material: mp 184–185°; $\lambda_{max}^{CHCl_3}$ 2.79, 2.86 (OH), 5.68 (CO), 8.42, 8.61, 10.00, 10.41, and 10.99 μ.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.32. Found: C, 70.8; H, 9.3.

(48) Beacon Chemical Co., Cambridge, Mass.

(4β,10β-Dimethyl-8β-hydroxy-5-octal-7β-yl)acetic Acid Lactone (30).[37c] A solution containing 462 mg of hydroxy lactone **29** in 12.5 ml of anhydrous pyridine was cooled in an ice bath while 1.25 ml of freshly distilled thionyl chloride was added.[37a] After stirring at 0° for 1.5 hr, the mixture was poured onto ice, treated with dilute hydrochloric acid, and thoroughly extracted with ether. The combined extracts were washed with aqueous sodium bicarbonate and saturated brine, dried,[37b] and concentrated under reduced pressure. The residue was distilled affording 414 mg (97%) of material, bp 85–95° (bath temperature) at 0.3 mm, which solidified. This material was used directly in the following experiment. A sample of the equivalent material obtained from a different experiment was sublimed at 30° (0.02 mm) giving lactone **30** as a white crystalline solid, mp 83–87°; $\lambda_{max}^{CCl_4}$ 5.63 (CO), 8.64, 9.57, 9.77, 9.96, 10.19, 10,90, and 11.03 μ; $\delta_{TMS}^{CCl_4}$ 5.23 (H-6 doublet, J = 3 cps), 4.48 (H-8 multiplet), 1.29 (C-10 CH$_3$), and 1.19 ppm (C-4 CH$_3$ doublet, J = 7 cps). One recrystallization from pentane afforded the analytical sample as needles, mp 90–91°.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 76.4; H, 9.2.

A gas chromatogram[49] of the sublimed material gave a single peak with a retention time of 6.4 min. The isomeric unsaturated lactone **13** has a retention time of 7.3 min under these conditions.

2-(4β,10β-Dimethyl-8β-hydroxy-5-octal-7β-yl)-2-propen-1-ol (32).[37c] The mineral oil was removed from 320 mg of 50% sodium hydride dispersion by three washings with heptane in a stream of nitrogen. A solution of 414 mg of the above lactone **30** in 16 ml of dimethyl carbonate containing a drop of methanol was immediately added, and the resulting mixture was heated to reflux with stirring for 5 hr.[37a] During this time a dense white precipitate formed and hydrogen was evolved. The dimethyl carbonate was removed by distillation under reduced pressure, and the dry solid residue was suspended in 35 ml of anhydrous 1,2-dimethoxyethane and treated with 320 mg of lithium aluminum hydride. The mixture was heated to reflux with stirring during 1 hr, 30 ml of anhydrous ether was added, and stirring was continued for 16.5 hr. Additional ether was added and the slurry was cautiously treated with 1.6 ml of water and stirred for 4 hr to allow the salts to granulate. The mixture was filtered with suction through a pad of Super-Cel, and the filter cake was suspended in fresh ether to remove adsorbed organic material and refiltered. The combined filtrates were concentrated under reduced pressure, and the residue, 410 mg of crystalline yellow solid, was recrystallized from heptane–ethyl acetate giving 150 mg (34%) of white solid diol **32**: mp 105–110°; $\lambda_{max}^{CHCl_3}$ 3.0 (OH), 3.26 (H-C=C), 6.09 (C=CH$_2$), 9.17, 9.46, 9.70, 10.11, 10.86, 11.06, 11.28, and 11.48 μ; $\delta_{TMS}^{CHCl_3}$ 5.46, 5.13 (H$_2$C=C), 5.34 (H-6 doublet, J = 5 cps), 4.19 (CH_2OH), 1.27 (C-10 CH$_3$), and 1.21 ppm (C-4 CH$_3$ doublet, J = 7 cps).

A sample was recrystallized twice from heptane–ethyl acetate giving white blades, mp 111–112°.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.21; H, 10.25. Found: C, 76.1; H, 10.1.

***dl*-Alantolactone (33).** A solution of 102 mg of diol **32** in 10 ml of dry benzene was stirred at room temperature with 1.5 g of activated manganese dioxide[48] for 6 hr. The mixture was filtered through a Super-Cel pad, the filter cake was thoroughly washed with ether and chloroform, and the combined filtrates were concentrated under reduced pressure. The residue was chromatographed on 10 ml of Florisil, and the fractions eluted with benzene and 10% ether in benzene were combined giving 80 mg (80%) of white crystalline alantolactone. The infrared and nmr spectra of this material were superimposable with the spectra of *d*-alantolactone.[4] A sample was recrystallized from pentane at −10° giving white needles, mp 58.5–59.5°, which were sublimed at 40° (0.05 mm) prior to combustion analysis.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.53; H, 8.69. Found: C, 77.7; H, 8.7.

A gas chromatogram[50] of this material showed a single peak with a retention time of 6.0 min, identical (peak enhancement) with that of *d*-alantolactone. These two compounds also exhibited identical mobilities on thin layer chromatography using silica gel.

Acknowledgment. We gratefully acknowledge support from the Public Health Service through a research

(49) A 10 ft × 0.25 in., 20% Carbowax 20M on Gas Pack F column was used at 225° with a helium flow rate of 190 ml/min.

(50) The Carbowax column[41] was used at 230° with a helium flow rate of 190 ml/min.

grant (AI-04965, Institute of Allergy and Infectious Diseases) and a predoctoral fellowship (5-Fl-GM-19,839, Institute of General Medical Sciences, to N. C.). We thank Professor W. S. Johnson and Dr. P. J. Neustaedter for their assistance with the olefinic cyclizations described in this report.

Hypochlorophyll

G. R. Seely

Contribution No. 213 from the Charles F. Kettering Research Laboratory, Yellow Springs, Ohio. *Received October 30, 1965*

Abstract: The photoreduction of chlorophyll and certain other phorbins by ascorbic acid, in pyridine containing ethanol and diazabicyclooctane, gives reduction products, named hypochlorophylls, which are believed to be 1,2-dihydromesochlorophylls. They are oxidized to mesochlorophylls by oxygen in the dark in the presence of weak acid or strong base, and by quinones and phenosafranine in the light. Their spectra closely resemble those of chlorins; in this respect, they are like the tetrahydroporphins from photoreduction of simple metallochlorins.

The photoreduction of simple metallochlorins, such as zinc chlorin[1] or zinc tetraphenylchlorin,[2] gives tetrahydroporphins with chlorin-like spectra, for which structures have been proposed having the β positions of two adjacent pyrrole rings reduced.[3] Chlorophyll or ethyl chlorophyllide a, on the other hand, gives a "tetrahydroporphin" ($ChlH_2$), with an absorption band at 525 mμ in pyridine,[4] the spectrum of which suggests that the closed, conjugated, double bond system characteristic of porphyrins has been interrupted. We wish to report that under certain conditions chlorophyll and other phorbins can be reduced to products that resemble the tetrahydroporphins from simple chlorins in their spectral and photochemical properties. To distinguish this class of reduction products from bacteriochlorins, which are tetrahydroporphins with opposite pyrrole rings reduced, we suggest that they be called *hypochlorins*, and the product from chlorophyll a, hypochlorophyll a. Their properties are still consistent with structures having adjacent pyrrole groups reduced.

The Hypochlorophyll Reaction

We earlier reported that certain aliphatic primary, secondary, and tertiary amines markedly accelerate and direct the course of photoreduction of zinc porphin by ascorbic acid.[1] It is difficult to use primary and secondary amines with chlorophylls, because of aminolytic attack on ring V (see structure Ia in Table I),[5] but tertiary amines are incapable of this reaction. After vain attempts to reduce protochlorophyll to chlorophyll in a manner analogous to the reduction of zinc porphin to zinc chlorin, we examined the effect of tertiary amines on the reduction of chlorophyll a itself.

The sequence of events during a typical reduction of chlorophyll a (Ia) or ethyl chlorophyllide a (Ib, which was used in place of chlorophyll for most of the experiments) in the presence of a rather strong ditertiary base, 1,4-diazabicyclo[2.2.2]octane (DABCO, Houdry Process and Chemical Co.), is shown in Figure 1. In red light, there first appeared the 525-mμ band of $ChlH_2$. In the absence of DABCO, this product accumulates and is the only reduction product of the chlorophyllide with noticeable absorption in the visible—the "Krasnovskii reduction."[4] In the presence of DABCO, this product reached a photostationary state, and the chlorophyllide was converted into another product with an absorption band at 632 mμ. The spectrum of this product, which we shall call ethyl hypochlorophyllide a, has narrow bands in the red and the violet regions, characteristic of porphyrins, and in fact resembles the spectra of certain Mg chlorins. Accompanying the bands of the hypochlorophyllide in Figure 1 is a band at 660 mμ, assigned to ethyl mesochlorophyllide for reasons soon to be evident, and a band, or shoulder, at 610 mμ, belonging to a by-product of unknown nature. There are bands in the violet belonging to these compounds at 434 and 415 mμ, respectively, though these are not prominent in Figure 1.

The conversion to hypochlorophyllide went best when the ethanol content of the solvent was 8–15% by volume. (This quantity is sufficient to "activate" chlorophyll toward the Krasnovskii reduction.[6]) Conversion was somewhat slower in pyridine containing DABCO but not ethanol; the proportion of mesochlorophyllide was larger, but the 610-mμ by-product was almost absent. At 60% ethanol, the yield of hypochlorophyllide was smaller because of Mg loss from $ChlH_2$. In ethanol without pyridine, reduction was very rapid in the presence of DABCO, but the only product was $ChlH_2$ (which rapidly lost Mg). The quantum yield was much larger than when pyridine was the activating base,[6] and probably exceeded 0.1.

DABCO is the best catalyst we have encountered for this reaction, but it is not unique. Reduction in ethanol produced some hypochlorophyllide in the presence of triethylamine, but not in the presence of hexamethylenetetramine or triethylenetetramine. Hypochlorophyllide appears to be a minor product of Krasnovskii re-

(1) G. R. Seely and K. Talmadge, *Photochem. Photobiol.*, **3**, 195 (1964).
(2) G. R. Seely and M. Calvin, *J. Chem. Phys.*, **23**, 1068 (1955).
(3) G. R. Seely, *ibid.*, **27**, 125 (1957).
(4) A. A. Krasnovskii, *Dokl. Akad. Nauk SSSR*, **60**, 421 (1948).
(5) H. Fischer and S. Goebel, *Ann.*, **524**, 269 (1936).
(6) G. R. Seely and A. Folkmanis, *J. Am. Chem. Soc.*, **86**, 2763 (1964).