C, 65.7; H, 9.4; N, 8.7.

When the same reaction was run keeping the temperature of the stirred mixture at 35–40° for 40 hr and 50° for 5 hr, 95% of the silane was consumed and the yields were: 35% of XI, 40% of XIV, 20% of XIII, and 5% of XII, based on 4-picoline reacted.

Silylation of 2-Picoline. When trimethylsilane was passed into a stirred suspension of Pd catalyst (10% on carbon) in dry 2-picoline in the same manner used for the other picolines, no reaction was observed. A faint trace (<1%) of reaction was observed after heating the material to 50° for 2 days, but the reaction was not continued to a point where any products could be isolated.

Hydrogenation of Products. Compounds II (44 mg), IV (45 mg), V (15.3 mg), and VII (50 mg) were hydrogenated in a micro-hydrogenation apparatus. Palladium catalyst (10% on charcoal) equal in weight to that of the compound was added to 10 ml of dry, O_2-free isooctane containing the material to be reduced. Quantitative absorption of H_2 in 5–10 min was observed for one double bond in II, and two double bonds in each of IV and V. Compounds II and IV gave material which had the same retention time as trimethylsilylpiperidine.

Compound VII took 15 hr for reduction and absorbed 80% of the theoretical amount for the five double bonds, going from a dark red to a colorless compound. Failure to get theoretical absorption was probably due to small amounts of oxidation that were extremely difficult to avoid.

Oxidation of N,N'-Bistrimethylsilyl-1,1'-dihydro-4,4'-bipyridine. Compound VII (0.764 g) was dissolved in 15 ml of anhydrous diethyl ether and dry air was bubbled through the solution for 4 min. The solution became yellow and after pulling off the volatiles (at 1 μ for 3 days) a mixture of tan crystals and a brown gum was obtained. From this mixture a 50% yield of 4,4'-bipyridine (white crystals, mp 111–113°) was obtained by recrystallization from isooctane.

Spectra. All ultraviolet spectra were recorded using a Cary recording spectrophotometer, Model 14, and made in dry, oxygen-free spectrograde cyclohexane.

Infrared data were obtained using a Perkin-Elmer 521 grating infrared spectrophotometer. The spectra were run on neat solutions in a microcell (0.15mm).

The proton magnetic resonance spectra were recorded with a Varian A-60 spectrometer. Measurements were made on 10–20% solutions in deuteriobenzene. Shifts were measured relative to the residual protons of deuteriobenzene. These have been converted to shifts relative to TMS by noting that the residual protons of deuteriobenzene appear 429 cps downfield from tetramethylsilane. The signals of the methylsilyl groups are not shown in the spectra of Figure 1 since they do not contribute to the elucidation of the structures.

Synthesis of 1-Epicyclocolorenone and Stereochemistry of Cyclocolorenone[1]

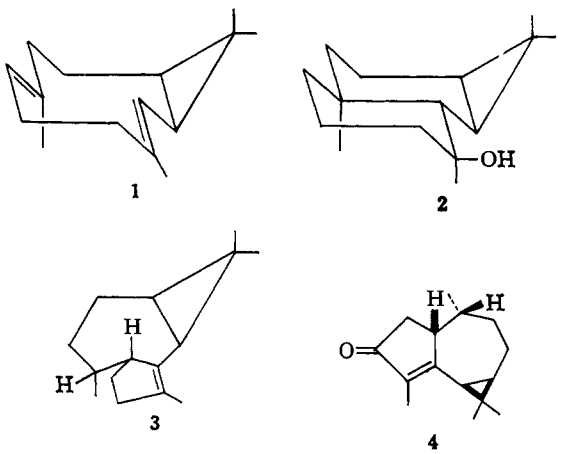
G. Büchi, Joel M. Kauffman, and H. J. E. Loewenthal[2]

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. *Received April 9, 1966*

Abstract: 1-Epicyclocolorenone (**22**) has been synthesized from O-acetylisophotosantonic acid lactone (**6**). With the aid of optical rotatory dispersion and proton magnetic and ultraviolet spectroscopy, the stereochemistry of the synthetic product was elucidated. The naturally occurring cyclocolorenone is unstable in relation to its C_1 epimer (**22**) and the former isomer consequently has the relative and absolute configuration shown in **21**.

The sesquiterpene ketone cyclocolorenone was first isolated from *Pseudowintera colorata*,[3] a shrub endemic to New Zealand and, more recently, from *Compositae* species.[4] Its gross structure was established some time ago[3] but both relative and absolute stereochemistry remained unknown.

We assumed that the cyclodecane derivative **1**[5] derived from all-*trans*-farnesol is involved in the biosynthesis of cyclocolorenone. As previously pointed out[5] transannular, antiplanar Markovnikov-oriented addition of water gives maaliol (**2**). If proton addition to the first double bond follows an anti-Markovnikov course and if the cyclization process terminates by proton loss, a tricyclic hydrocarbon (**3**) results which subsequently could be oxidized to cyclocolorenone (**4**).



1 2 3 4

To provide experimental support for the stereochemical consequences of this suggestion, we attempted a synthesis of cyclocolorenone (**4**), and the readily available O-acetylisophotosantonic acid lactone (**6**)[6] was chosen as starting material. Treatment with concentrated sulfuric acid gave the previously described dienone lactone **7**[6] identical with a sample prepared

(1) Preliminary communication: G. Büchi and H. J. E. Loewenthal, *Proc. Chem. Soc.*, 280 (1962).

(2) On leave from the Israel Institute of Technology.

(3) R. E. Corbett and R. N. Speden, *J. Chem. Soc.*, 3710 (1958).

(4) J. Krepinsky and V. Herout, *Collection Czech. Chem. Commun.*, 27, 2459 (1962).

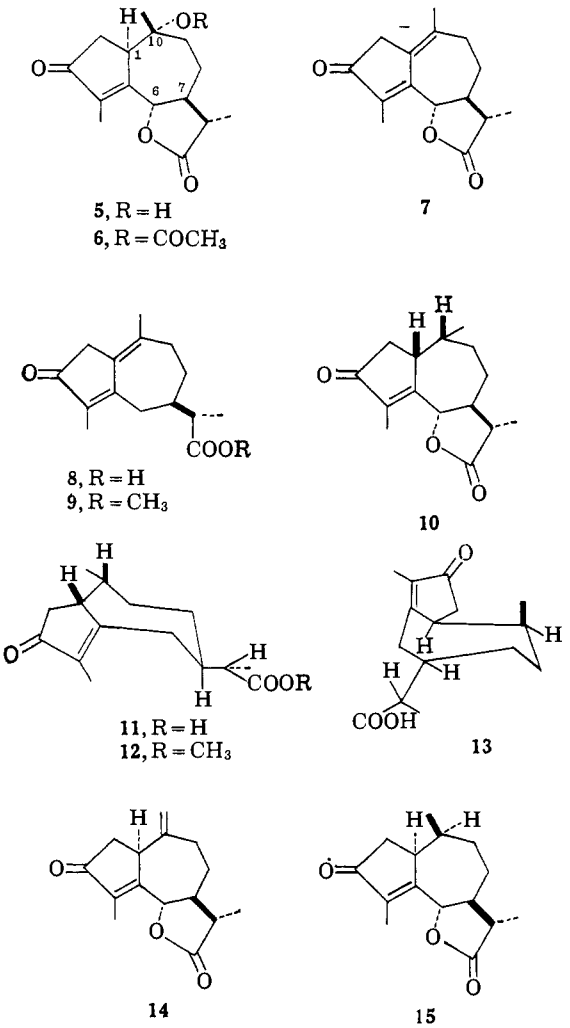
(5) R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Am. Chem. Soc.*, **82**, 2327 (1960). Other cyclodecanes have been previously proposed as biogenetic precursors of cyclic sesquiterpenes: L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953); D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 150 (1957); J. B. Hendrickson, *Tetrahedron*, 7, 82 (1959).

(6) D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 929 (1957).

from lumisantonin.[7] Hydrogenolysis of the allylic lactone function was effected by the action of chromous chloride[8] in acetic acid giving the dienone carboxylic acid **8** which was also prepared by Barton and coworkers using a similar route.[9a] Catalytic reduction of this acid under a variety of conditions was selective in that only the C_1–C_{10} double bond was reduced, but in each case the product was a mixture of keto acids separable by fractional crystallization. The minor product was also available by an alternate route. Dehydration of isophotosantonic acid lactone (**5**) with thionyl chloride in pyridine furnished the exocyclic olefin **14**.[6] Selective hydrogenation gave the lactone **15** which in turn was hydrogenolyzed to the carboxylic acid **13**. Significantly, the epimeric lactone **10**[9b] itself prepared by selective hydrogenation of the dienone **7** was stable to chromous chloride, again confirming the observation that reductions of this type are greatly influenced by stereoelectronic factors.[9a]

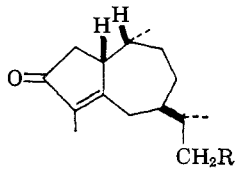
The following conclusions can be drawn regarding the structures and geometries of the two carboxylic acids **11** and **13**. Both display intense ultraviolet absorptions at 242 mμ and both are cyclopentenones as indicated by infrared absorptions at 1685 and 1640 cm^{-1}. The synthesis of one acid (**13**) from the methylene lactone **14** demonstrates that the configuration at C_1 is identical with that of isophotosantonic acid lactone (**5**), and this conclusion is supported by the optical rotatory dispersion curve of acid **13** which is very similar to that of isophotosantonic acid lactone (**5**).[10] At the outset of this study it was assumed that isophotosantonic acid lactone has the C_1-β configuration proposed by earlier workers,[10] but evidence against this assignment was subsequently provided by a complete X-ray analysis of bromodihydroisophotosantonic acid lactone[11] and independently by an analysis of the proton spectra of the two acids **11** and **13**. The spectrum of the major isomer **11** produced on catalytic reduction of the diene **8** exhibits a methyl doublet with the anticipated chemical shift of 0.97 ppm. In the epimer **13** the methyl protons are diamagnetically shifted to 0.62 ppm by the olefinic double bond. Such abnormal shielding is *a priori* only possible in the two epimers having the hydrogen atoms at C_1 and C_{10} in a *cis* orientation, and if the two structures are analyzed in conformational terms it is noticed that only one of the two meets these chemical shift considerations. The most stable conformation of one isomer is represented by **13** which displays the cycloheptane ring containing one sp^2-carbon atom in a chair conformation and the propionic acid and methyl side chains in equatorial and axial orientations, respectively. The second isomer on the other hand appears most stable in conformation **11** with both substituents equatorially oriented and the cycloheptane ring in a slightly distorted chair conformation.[12] Long-range shielding of the methyl protons by the double bond is only possible in isomer **13** and we conclude that this structure represents the minor product formed on catalytic reduction of the dienone **8**. The previously described relationship of the acid **13** with isophotosantonic acid lactone (**5**) demands a C_1-α configuration also in the latter substance. If we assume *cis* addition of hydrogen from the more accessible β side of the diene **8** the major product formed in the reduction should have structure **11**. This presumption found support, at least as far as the configuration at C_1 is concerned, from the optical rotatory dispersion curve which is the virtual mirror image of that of the carboxylic acid **13**. Consequently intermediate **11** has the stereochemistry desired and we proceeded with its further transformation to cyclocolorenone (**4**).

Methylation with diazomethane yielded the methyl ester **12** which incidentally was available in superior yield by catalytic reduction of the dienone ester **9** prepared by methylation of the corresponding acid **8**. Reduction with lithium aluminum hydride gave a mixture of crystalline C_3-epimeric diols which was partially reoxidized with dichlorodicyanobenzoquinone[13] giving the crystalline hydroxy ketone **16**. Oxidation with manganese dioxide gave to a large extent what appeared to be an aldehydo ketone, a result similar to that ex-

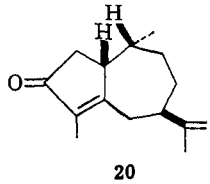


(7) D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O. Jeger, and L. J. Krebaum, *Helv. Chim. Acta*, 40, 1732 (1957).
(8) W. Cole and P. L. Julian, *J. Org. Chem.*, 19, 131 (1954).
(9) (a) D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962); (b) D. H. R. Barton, J. T. Pinhey, and R. J. Wells, *ibid.*, 2518 (1964).
(10) C. Djerassi, J. Osiecki, and W. Herz, *J. Org. Chem.*, 22, 1361 (1957).
(11) J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, 111 (1962).
(12) The conformational analysis of hydroazulenic sesquiterpenes was discussed by J. B. Hendrickson, *Tetrahedron*, 19, 1387 (1963).
(13) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, No. 9, 14 (1960); S. H. Burstein and H. J. Ringold, *J. Am. Chem. Soc.*, 86, 4952 (1964).

perienced with an analogous diol in the santonin series.[14] Oppenauer oxidation with acetone in the presence of aluminum isopropoxide was the method of choice and furnished reproducible yields ranging from 70 to 80%. Conversion of the alcohol **16** to its *p*-bromobenzenesulfonate (**17**) was effected using brosyl anhydride rather than the more conventional brosyl chloride which led to the formation of considerable quantities of primary chloride. Exposure of the brosylate to dimethylamine produced the crystalline dimethylamino ketone (**18**) whose optical rotatory dispersion curve was very similar to that of the precursor **11**, indicating unchanged configuration at C_1. Pyrolysis[15] of the corresponding N-oxide (**19**) gave the liquid olefin **20**.

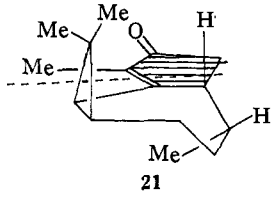


16, R = OH
17, R = $OSO_2C_6H_4Br$
18, R = $N(CH_3)_2$
19, R = $\overset{\downarrow}{N}(CH_3)_2$ O

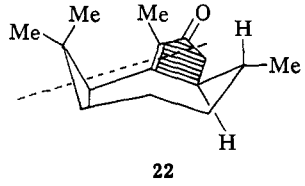


20

Construction of the cyclopropane ring proceeded smoothly when the crude tertiary bromide prepared by addition of hydrobromic acid to the olefin **20** was subjected to the action of methanolic alkali.[5] Chromatographic purification of the resulting product gave a crystalline substance whose infrared spectrum is strikingly similar to that of cyclocolorenone and the mass spectra of the two compounds differ only in the relative intensities of a few peaks. However, the ultraviolet spectrum (λ_{max} 253 mμ) and optical rotation ([α]D −167°) were very different from those of natural cyclocolorenone (λ_{max} 262 mμ, [α]D −466°) and moreover the proton magnetic resonance spectra of the two substances show significant differences.



21



22

On the supposition that a sample of cyclocolorenone kindly provided by Corbett might be impure we subjected it to chromatography on alumina. This resulted to the extent of over 60% in conversion to a crystalline transformation product identical in all respects with our synthetic product. Interestingly, no change occurred on chromatography on Florisil but essentially complete epimerization is brought about also by alkali.[16] It is thus clear that cyclocolorenone (**4**) is unstable in respect to its C_1 epimer **22** and under these circumstances the configuration of the epimerizable center in these two

(14) H. Bruderer, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **39**, 858 (1956).
(15) A. C. Cope and E. R. Trumbull, *Org. Reactions*, 11, 317 (1960).
(16) Private communication by Professor R. E. Corbett. See also R. E. Corbett and H. Young, *Australian J. Chem.*, 16, 250 (1963).

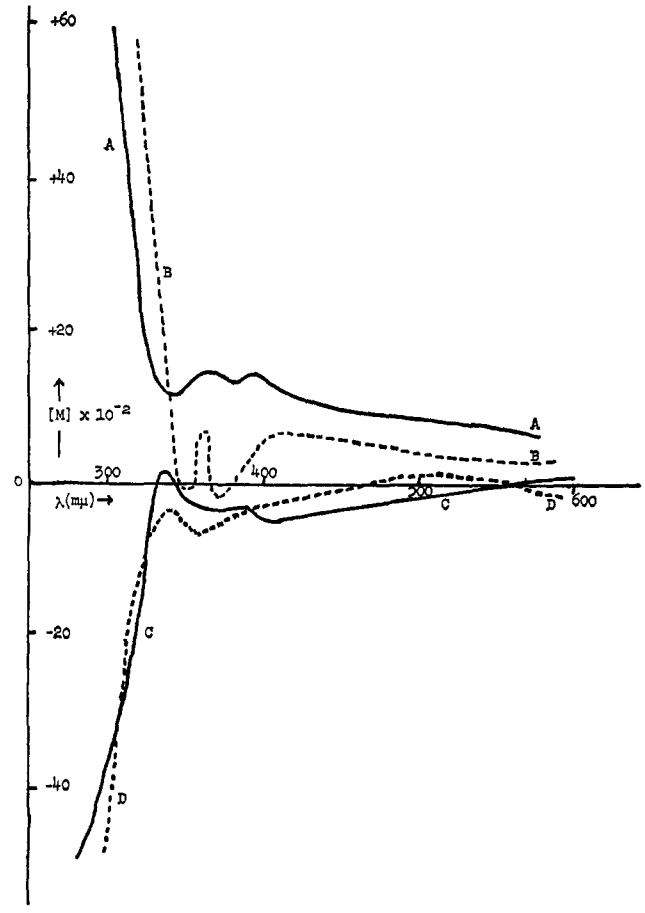


Figure 1. Optical rotary dispersion curves: A (———) isophotosantonic lactone **5**; B (– – – –) keto acid **13**; C (———) keto acid **11**; and D (– – – –) amino ketone **18**.

compounds does not follow from those of the synthetic precursors. Evidence concerning the geometry of this center is provided by the ultraviolet light absorption properties of the two isomers. Both experimental findings[17] and theoretical considerations[18] indicate that interaction between the cyclopropane ring and the π system in a β-cyclopropyl α,β-unsaturated ketone is most effective when the plane of the ring and the p orbitals of the α,β-carbonyl grouping are parallel. Stability considerations indicate that the isomer with C_1-β configuration is most stable in the molecular arrangement (**21**) with a boat cycloheptane ring. The conformer with lowest energy of the more stable C_1 epimer has the cycloheptane ring in a chair conformation (**22**). The angles between the plane of the α,β-unsaturated ketone grouping and the plane of the cyclopropane ring are estimated from Dreiding models to be 65° in **21** and 50° in **22**, and we conclude that cyclocolorenone and 1-epicyclocolorenone have the configurations indicated in **21** and **22**, respectively. It will be recalled that the stereochemistry at C_{10} in the synthetic intermediates was assigned on grounds of *cis* hydrogenation of the dienonones **8** and **9** only, but much needed additional evidence on this point was provided by the proton spectra of cyclocolorenone (**21**) and its epimer (**22**). The C_{10}-methyl group in the former gives rise to a doublet at high field (0.78 ppm) and hence its

(17) E. M. Kosower and M. Ito, *Proc. Chem. Soc.*, 25 (1962).
(18) R. Hoffmann, *Tetrahedron Letters*, 3819 (1965).

protons must be situated below the plane of the enone chromophore. Such shielding again is only possible when the two hydrogens at C_1 and C_{10} are *cis* oriented. The corresponding signal in the spectrum of epicyclocolorenone (**22**) has moved downfield (1.02 ppm) and merged partly with the singlet caused by one of the geminal methyl groups. It is no longer a doublet but a broad band with an inflexion on the low-field side and this can be ascribed to a small difference in chemical shift between methine and adjacent methylene protons, the methine proton being shifted upfield by long-range shielding from the double bond. An entirely analogous situation has been encountered with lycodine and related alkaloids.[19] Attempts to reconvert epicyclocolorenone (**22**) to cyclocolorenone (**21**) by rate-controlled protonation of the corresponding enolate met with no success and the synthesis of cyclocolorenone (**21**) remains to be accomplished.

A conversion of the sesquiterpene hydrocarbon α-gurjunene[20] to cyclocolorenone (**21**) demonstrated identical configurations at all four asymmetric carbon atoms in the two natural products and established stereostructure **3** for α-gurjunene.

Experimental Section

Microanalyses were performed by Dr. S. M. Nagy and associates at the M.I.T. Microanalytical Laboratory. Melting points are corrected and were taken on a Kofler hot-stage microscope. Ultraviolet spectra were determined in methanol using a Cary Model 11 recording spectrophotometer. Infrared spectra were measured on a Perkin-Elmer Model 21 recording spectrophotometer with sodium chloride optics, unless otherwise specified. The listings of infrared bands include those which are relevant to the structural argument and other medium and strong bands. A Varian Associates A-60 was used for recording nuclear magnetic resonance data, and peak positions are given as δ values in ppm from TMS. Thin layer chromatograms on 1 × 3 in. microscope slides coated with silica gel G were distributed with 1% ethanol–chloroform and developed with iodine vapor. Evaporations of solvents were performed at 50–60 mm with a Labline rotary evaporator.

O-Acetylisophotosantonic Acid Lactone (6). A solution of α-santonin (25 g, 0.1 mole) in 420 ml of acetic acid was degassed at 50 mm and placed in a 500-ml Kjeldahl flask, which was modified by the addition of a side arm to accept a reflux condenser in addition to a high-pressure, 100-w, Hanau mercury-arc lamp inside a quartz tube. The irradiation was performed under nitrogen, with brisk magnetic stirring, and with aluminum foil wrapped around the flask. After approximately 1 hr of lamp operation, the solvent began to reflux. The brown polymer which accumulated on the surface of the quartz jacket surrounding the Hanau lamp was destroyed every 8 hr by removing the lamp from the Kjeldahl flask and irradiating nitric acid until the polymer was oxidized. After washing with water, ammonia, and acetone, the dried lamp was returned to the warm reaction mixture. After a 24-hr reaction period, the dark products from three such runs were combined and concentrated at 80° (55 mm). The brown residue was dissolved in 450 ml of methylene chloride, washed with 600 ml of ice-cold 5% sodium hydroxide and two 200-ml portions of water, dried over sodium sulfate, and freed of solvent. The residual dark oil (70.5 g, 75%) was crystallized from 500 ml of 2-propanol and the product was dried at 80° (55 mm) to give 30.0 g (32%) of white spars, mp 175–183° (lit.[6] mp 175–177° from ethyl acetate–ligroin).

The combined mother liquors and washings from 10 runs (2 l.) were passed through 200 g of Woelm activity I alumina, followed by 0.5 l. of 95% ethanol. The total eluate was concentrated to 0.5 l., cooled in ice, and seeded. After prolonged cooling in ice–salt, 30 g (10%) of product separated, mp 175–183°. This was recrystallized from 280 ml of 2-propanol with about 60% recovery, to give an over-all yield of 38%.

The nmr sample was prepared by recrystallization from 95% ethanol and had mp 182–182.5°; δ ($CDCl_3$) 1.10 (3 H), 1.25 (3 H, doublet, J = 6.5 cps), 1.54 (1 H, diffuse), 1.85 (3 H, triplet, J = 1.5 cps), 2.02 (3 H), 2.02–2.63 (7 H, diffuse), 4.13 (1 H, diffuse), 4.92 (1 H, doublet, J = 9.5 cps).

Dienone Lactone 7. Sulfuric acid (300 ml) in a 60-ml Berzelius beaker was cooled in ice and stirred mechanically with vigor. Lactone **6** (30 g, 0.098 mole) was pulverized and added in small portions at 5–10° during 10 min to the sulfuric acid. After an additional 45 min of stirring, nearly all the acetate had dissolved and the mixture was poured onto 3 kg of ice. When most of the ice had melted, the suspension was extracted with two 150-ml portions of methylene chloride, and the extract was washed with 300 ml of ice-cold 5% sodium hydroxide, then 300 ml of water, dried with sodium sulfate, and freed of solvent. The residual, clear oil was crystallized from 200 ml of 25% methanol–isopropyl ether to give 19.1 g (80%) of long needles, mp 93–98°. This compound had to be stored in brown glass because it is rapidly decomposed by ordinary fluorescent room light. The use of twice-recrystallized acetate raised the yield to 91%, mp 97.5–98.5°; $\nu_{max}^{CCl_4}$ 2980, 2912, 2860, 1772 (s), 1685 (s), 1590, 1460, 1395, 1315, 1240, 1165 (s), 1080, 1030, and 1000 cm^{-1} (lit.[7] mp 97–98°; λ_{max} 304 mμ (ε 13,800); ν_{max}^{KBr} 1780, 1688, and 1597 cm^{-1}).

Catalytic Reduction of Dienone Lactone 7 to Lactone 10. Lactone **7** (246 mg, 1 mmole) in 8 ml of tetrahydrofuran was hydrogenated in the presence of 20 mg of 7% palladium-on-strontium carbonate catalyst until uptake ceased after the absorption of 1.05 moles of hydrogen (15 min). The lactone obtained after filtration and removal of solvent was crystallized from chloroform–isopropyl ether to give 201 mg (81%), mp 153–153.5°; $[\alpha]D$ −118 ± 5°; $\nu_{max}^{CHCl_3}$ 2918, 1775 (s), 1700 (s), 1647, 1460, 1385, 1305, 1230, 1172, 1156, 1142, 1117, 1087, 1035, and 1000 cm^{-1}; λ_{max} 239.5 mμ (ε 13,800).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.45; H, 8.2.

Dienone Carboxylic Acid (8). A solution of chromous chloride was prepared by the rapid addition of chromic chloride hexahydrate (120 g, 0.47 mole) to amalgamated zinc[21] (from 50 g of zinc dust) under 600 ml of water containing 15 ml of hydrochloric acid. Carbon dioxide was bubbled rapidly through the mixture which was also shaken occasionally. After about 1 hr the initial dense green color changed to pale blue. Meanwhile, a solution of the dienone lactone **7** (20.5 g, 0.0833 mole) in 250 ml of acetic acid was degassed at 50 mm and warmed to 45° with magnetic stirring. The blue chromous chloride solution was added dropwise during 1.5 hr with rigorous exclusion of air by carbon dioxide, and stirring at 45° was maintained for another 14 hr. Half the solvent was distilled quickly at 90° (55 mm), then the cooled residue was diluted with 350 ml of water and extracted with three 100-ml portions of methylene chloride. The combined extracts were washed with 100 ml of water and treated with 200 ml of ice-cold sodium hydroxide (5%). The basic layer was acidified with a slurry of 22 ml of hydrochloric acid in 20 g of ice, and the product, which separated as an oil, was taken up in 200 ml of warm benzene, dried for a short time with magnesium sulfate, freed of solvent, and crystallized from 100 ml of 5% methanol–isopropyl ether. After several hours at −10° the product[22] was filtered and dried at 52° (55 mm) for 2 hr to give 15.6 g (73%) of white rhomboids, mp 110–112°; the analytical sample was obtained by two recrystallizations of the oil from methylene chloride–isopropyl ether, mp 109–110°; $[\alpha]D$ +107 ± 3° (*c* 0.865, MeOH); λ_{max} 305 mμ (ε 15,400); $\nu_{max}^{CHCl_3}$ 2960, 2910, 1700 (s), 1673 (s), 1592, 1392, 1285, and 1220 (broad) cm^{-1} (lit.[9a] mp 106–108°, $[\alpha]D$ +112°).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.37; H, 8.17.

The menthol fraction from this reduction gave the lactone **10**.

Catalytic Reduction of Dienone Acid 8 to Acid 11. To 100 mg of prehydrogenated 7% palladium-on-strontium carbonate catalyst in 5 ml of 95% ethanol was added dienone acid **8** (496 mg, 2 mmoles) in a mixture of 2.5 ml of 1 *N* sodium hydroxide and 1.5 ml of ethanol. Uptake of hydrogen was complete in 23 min (46 ml,

(19) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

(20) P. Pesnelle and G. Ourisson, *J. Org. Chem.*, **30**, 1744 (1965); M. Palmade, P. Pesnelle, J. Streith, and G. Ourisson, *Bull. Soc. Chim. France*, 1950 (1963); J. Streith and G. Ourisson, *ibid.*, 1960 (1963).

(21) P. D. Caesar, *Org. Syn.*, **33**, 47 (1953). The amalgamated zinc was not filtered, but instead was washed by decantations with distilled water.

(22) This compound is sensitive to heat, light, and air, and had to be stored in dark glass under carbon dioxide below 20°.

2.05 mmoles, 103%). Acetic acid was added to the filtered mixture until its pH was 5, and the ethanol was evaporated. The aqueous solution which remained was extracted with methylene chloride, and the extract was dried over magnesium sulfate, freed of solvent, and crystallized from 10 ml of isopropyl ether to give 195 mg (39%), mp 130–141°. Two recrystallizations from methylene chloride–isopropyl ether produced an analytical sample, mp 135.5–136.5°; $[\alpha]D$ −43 ± 5° (*c* 0.87 MeOH); λ_{max} 242 mμ (ε 14,600); $\nu_{max}^{CHCl_3}$ 2920, 1700, 1685, 1640, 1463, 1387, 1348, 1287, and 1234 cm^{-1}; δ ($CDCl_3$) 0.97 (3 H, doublet, *J* = 8 cps), 1.25 (3 H, doublet, *J* = 7.5 cps), 1.02–1.62 (3 H, diffuse), 1.72 (3 H, doublet, *J* = 3.5 cps), 1.75–2.60 (6 H, diffuse), 2.68 (1 H), 2.91 (2 H, diffuse).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 8.84.

Carboxylic Acid 13. A. A small amount of this compound was obtained from the mother liquors of the above keto acid **11**. After fractional crystallization and sublimation, it was identical with the product from method B as shown by mixture melting point determination and comparison of infrared and nmr spectra.

B. Catalytic hydrogenation of lactone **14**[6] (323 mg, 1.31 mmoles) in 10 ml of ethyl acetate over 14 mg of 10% palladium-on-charcoal catalyst until uptake of hydrogen ceased (1.01 mole equiv after 18 min) produced an amorphous lactone **15**, $[\alpha]D$ +200°; $\nu_{max}^{CHCl_3}$ 2918, 1777, 1698, 1305, 1230, 1174, and 895 cm^{-1}; δ ($CDCl_3$) 0.69 (3 H, doublet, *J* = 7 cps), 0.87–1.14 (1 H, diffuse), 1.27 (3 H, doublet, *J* = 6.5 cps), 1.32–2.92 (8 H, diffuse), 1.87 (3 H, triplet, *J* = 1.5 cps), 3.15 (1 H, diffuse), 4.88 (1 H, diffuse doublet, *J* = 8.5 cps).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.43; H, 8.11.

Crude lactone **15** (185 mg, 0.747 mmole) dissolved in 4 ml of acetic acid was reduced with chromous chloride as described for lactone **7** using proportionate amounts of reactants. The acidic fraction from the reduction (93 mg) was crystallized from hexane–isopropyl ether to give the keto acid **13**, mp 136–136.5°; λ_{max} 242.5 mμ (ε 13,600); $\nu_{max}^{CHCl_3}$ 2910, 1700 (shoulder), 1682 (s), 1627, 1385, and 1220 cm^{-1}; δ ($CDCl_3$) 0.62 (3 H, doublet, *J* = 7 cps), 1.22 (3 H, doublet, *J* = 7 cps), 1.3–3.1 (11 H, diffuse), 1.67 (3 H), 3.12 (1 H).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.72; H, 8.91.

Methyl Ester 9 of Dienonecarboxylic Acid (8). Diazomethane from 28.8 g of N,N-dimethyl-N,N-dinitrosoterephthalamide was slowly added to a suspension of dienone acid **8** (20 g, 0.080 mole) in 75 ml of cold ethyl acetate, with rapid stirring and occasional cooling in ice. The acid dissolved during the addition, which was continued only until the yellow color persisted. The mixture was boiled to remove excess diazomethane and concentrated at 60° (50 mm). The residual oil was crystallized from 200 ml of hexane at −10° and dried at 25° (1 mm) for 2 hr[22] to give 20.3 g (95%) of large spars, mp 62–63°. One recrystallization from ligroin–ether gave an analytical sample, mp 62.7–63.6°; λ_{max} 304 mμ (ε 15,400); $\nu_{max}^{CCl_4}$ 1740, 1700, 1600, 1200, and 1160 cm^{-1} (Perkin-Elmer 237).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.17; H, 8.52.

Catalytic Reduction of Methyl Ester 9. Dienone methyl ester **9** (20 g, 0.077 mole) was hydrogenated in 125 ml of ethyl acetate over 500 mg of 10% palladium-on-charcoal catalyst at 25° (755 mm) for 45 min. Hydrogen uptake corresponded to 1825 ml (1660 ml cor, 0.074 mole, 96%). The clear oil which remained after filtration and removal of solvent was crystallized from 200 ml of hexane at −10°. The large cubical crystals of **12** were dried at 50° (55 mm) for 10 hr to give 12.6 g (62%), mp 78–80°. The infrared spectrum was identical with ester prepared by methylating acid **11**. An analytical sample from the latter route had mp 77.5–79°; λ_{max} 242 mμ (ε 14,600); $\nu_{max}^{CHCl_3}$ 2920, 1725, 1687, 1637, 1462, 1440, 1347, 1196, and 1160 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.50; H, 9.15.

Reduction of Methyl Ester 12 with Lithium Aluminum Hydride. Pulverized lithium aluminum hydride (2.0 g, 0.053 mole) was covered with 25 ml of ether and the mixture was heated to reflux. Methyl ester **12** (5.0 g, 0.019 mole) in 75 ml of ether was added during 15 min, and heating was continued for 2 hr. Saturated sodium sulfate solution (10 ml) was added dropwise, the resulting precipitate was filtered, the solvent was evaporated to give an oil (4.9 g), and the oil was crystallized slowly from 50 ml of isopropyl ether at −10°. The yield of mixed diols was 3.0 g (70%), mp 105–110°; $\nu_{max}^{CCl_4}$ 3625, 3400, 2960, 2920, 2870, 1460, and 1385 cm^{-1} (Perkin-Elmer 237). The mother liquors were used to crystallize subsequent batches which raised the yield to 90%.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 76.10; H, 10.92.

Oxidation to Hydroxy Ketone 16. A mixture of 500 ml of benzene, 100 ml of reagent grade acetone, 25 g of aluminum isopropoxide, and diols (10.0 g, 0.042 mole) was stirred at 38° for 24 hr, and subsequently washed with 300 ml of ice-cold 4% hydrochloric acid. These washings were extracted with 100 ml of benzene. The combined benzene solutions were washed with 200 ml of ice-cold 4% hydrochloric acid and 100 ml of 5% sodium bicarbonate, dried with magnesium sulfate, and concentrated at 60° (55 mm). The residual oil was crystallized from 100 ml of 35% hexane–isopropyl ether at −12° to give 8.0 g (81%), mp 50–52°; $\nu_{max}^{CHCl_3}$ 3625, 3240 (broad), 2920, 1685, 1635, 1465, 1375, 1345, and 1050 cm^{-1} (Perkin-Elmer 237).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.71; H, 10.11.

In subsequent runs, crystallization occurred readily on seeding, but in the first run the oil had to be purified further as follows. It was heated under reflux with 100 ml of 95% ethanol, 3 ml of acetic acid, and 2.0 g of Girard's reagent T for 2 hr, cooled, and shaken with 10% aqueous sodium sulfate and ether. The organic layer was carefully dried and would then produce a crystalline product on dilution with hexane and cooling. Under these conditions, the impurities combine with Girard's reagent but the product does not.

Brosylate 17. A bath containing isobutylene under reflux was used to cool 230 ml of dry pyridine to −5°. With strong mechanical stirring, brosyl anhydride[23] (31 g, 0.068 mole) was added at once, and the mixture was cooled and stirred for 15 min. Hydroxy ketone **16** (13.2 g, 0.056 mole) in 30 ml of pyridine was added dropwise during 20 min. After an additional period of 4.5 hr at 15°, the mixture was poured into 500 ml of hydrochloric acid, 500 ml of water, 600 ml of chopped ice, 400 ml of benzene, and 150 ml of hexane. The organic layer was washed with 100 ml of 5% sodium bicarbonate and 100 ml of saturated sodium sulfate, dried over magnesium sulfate, and poured onto a column containing 200 g of Merck acid-washed alumina. Two liters of 10% chloroform–benzene was then passed through the column, and the total eluate, following removal of solvents, was crystallized from 200 ml of 10% chloroform–isopropyl ether to give 17.0 g (67%), mp 79–82°; $\nu_{max}^{CHCl_3}$ 1695, 1640, 1180, 960, and 820 (broad) cm^{-1} (Perkin-Elmer 137). One recrystallization from 2-propanol–isopropyl ether gave the analytical sample, mp 82–85°.

Anal. Calcd for $C_{21}H_{27}BrO_4S$: C, 55.38; H, 5.98. Found: C, 54.86; H, 6.17.

Dimethylamino Ketone 18. A 200-ml pressure flask was cooled in ice, charged with the brosylate **17** (3.64 g, 8 mmoles) and approximately 25 ml of anhydrous dimethylamine, sealed, heated at 55° for 7 hr, cooled in ice, opened, and left at 20° overnight so that excess dimethylamine could evaporate. Chloroform was used to wash out the crude product, which was freed of solvent and partitioned between 80 ml of 4% hydrochloric acid and two 25-ml portions of isopropyl ether. The aqueous layer was treated with 80 ml of ice-cold 5% sodium hydroxide, then extracted with two 50-ml portions of chloroform. These extracts were dried with magnesium sulfate and poured through 50 g of Merck alumina, followed by 100 ml of chloroform. Solvent-free eluate was crystallized from 4 ml of isopropyl ether–10 ml of hexane on Dry Ice to give 1.40 g of light yellow spars, mp 47–50°. An analytical sample was prepared by recrystallization from pentane at −30°, mp 48.5–49°; $[\alpha]D$ −44 ± 3° (*c* 0.97, MeOH); λ_{max} 243.5 mμ (ε 15,100); $\nu_{max}^{CHCl_3}$ 2920, 2765, 1685, 1637, 1465, 1387, and 1347 cm^{-1}.

Anal. Calcd for $C_{17}H_{29}NO$: N, 5.33. Found: N, 5.35.

Unsaturated Ketone 20. A solution of tertiary amine **18** (2.63 g, 10 mmoles) in 10 ml of chloroform and a solution of perbenzoic acid (10 mmoles) in 21 ml of chloroform were cooled with Dry Ice for 20 min, when the former was added to the latter. The mixture was stored at −10° overnight, diluted with 20 ml of chloroform, washed with 50 ml of 30% potassium carbonate and 50 ml of half-saturated sodium sulfate, dried over magnesium sulfate, and evaporated to leave 2.27 g (81%) of thick, oily amine oxide **19**; $\nu_{max}^{CHCl_3}$ 1690 (s), 1640, 1448, 1385, 1228, 1182, and 1100 cm^{-1} (Perkin-Elmer 237). Thin layer chromatography showed the presence of a single substance with R_f 0.2 while the starting material had R_f 0.7.

The amine oxide was heated in a Hickman still at a bath temperature of 100–150°, using a trace of phenothiazine as a polymerization inhibitor. The distillate was taken up in hexane, washed with 25

(23) Made by the procedure used for the preparation of tosyl anhydride: L. Field and P. H. Settlage, *J. Am. Chem. Soc.*, 76, 1222 (1954).

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.