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Synthetic Study of Siccanin, an Antifungal Antibiotic. I. Synthesis of 3,5a-Dimethyl-1-hydroxy-5,5a,6,7,8,8a-hexahydroxanthene

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Refering to the previous work,[2] the tetracyclic diol (**3a**) derived from siccanin (**1**), an antifungal antibiotic, was converted back into **1**; and **3a** was shown as an important synthetic intermediate for **1**. On the other hand, as a preliminary study on synthesis of **1**, cyclization of 1-methyl-2-(2,6-dihydroxy-4-methylbenzyl)cyclohexanol (**19** or **20**) or 1-methylene-2-(2,6-dihydroxy-4-methylbenzyl)cyclohexane (**21**) was carried out, forming a hexahydroxanthene derivative (**23**) whose structure involves the **B**, **C**, and **D** rings of siccanin (**1**).

The antibiotic siccanin, a fermentation product of *Helminthosporium siccans* DRECHSLER, has been shown to exhibit widespread inhibitory activity against a variety of fungi; it has especially strong activities against *Trichophyton interdigitale* and *T. asteroides* at 0.8—6.3 μg/ml and has already been used for clinical trials against superficial fungal infections.[3] Chemical studies including X-ray analysis on siccanin[3,4] have revealed its triprenylphenol structure (**1**) involving a bicyclic sesquiterpene moiety, which contains a characteristic *cis/syn/cis* ring juncture; thus it is of interest as the first member of a naturally occuring drimane skeleton. This paper describes preliminary work on a synthetic approach directed towards siccanin.[5]

In the course of chemical studies on siccanin, Hirai, *et al.*[2] have found that treatment of siccanin (**1**) with acetic anhydride in the presence of boron trifluoride etherate yielded a tetracyclic triol triacetate (**2**) and the latter easily reformed **1** on treatment with base. Further, they reported that reduction of siccanin (**1**) with lithium aluminum hydride in the presence of aluminum chloride afforded a tetracyclic diol (**3a**) and they also succeeded in introducing an oxygen function again in the benzylic position of a tetracyclic compound (**4**) derived from **3a** by chromic anhydride oxidation to prepare a ketone compound (**5**). Prior to attempting a siccanin synthesis, it was first presumed that the tetracyclic diol (**3a**) would be an important synthetic intermediate. However, conversion of **3a** into siccanin (**1**) has not been reported; therefore, we pursued the procedures of Hirai, *et al.*[2] and investigated the possibility of filling this experimental gap. This supplementary study is also one topic covered in this paper.

The tetracyclic diol (**3a**) which was prepared by the known method[2] formed a syrupy diacetate (**3b**). Oxidation of the benzylic methylene group of **3b** was carried out by treatment with chromic anhydride and afforded a crystalline ketodiol diacetate (**6a**), mp 178.5—

1) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
2) K. Hirai, K.T. Suzuki, and S. Nozoe, *Tetrahedron*, **27**, 6057 (1971).
3) K. Ishibashi, K. Hirai, M. Arai, S. Sugawara, A. Endo, A. Yasumura, H. Masuda, and T. Muramatsu, *Ann. Sankyo Res. Lab.*, **22**, 1 (1970) and references cited therein.
4) K. Hirai, S. Nozoe, K. Tsuda, Y. Iitaka, K. Ishibashi, and M. Shirasaka, *Tetrahedron Letters*, **1967**, 2177; K. Hirai, S. Okuda, S. Nozoe, and Y. Iitaka, *Acta Crystallographica B*, **25**, 2630 (1969).
5) In connection with synthesis of siccanochromenes, Nozoe, and Hirai has announced an ingenious synthetic approach for siccanin. See S. Nozoe and K. Hirai, *Tetrahedron*, **27**, 6073 (1971).

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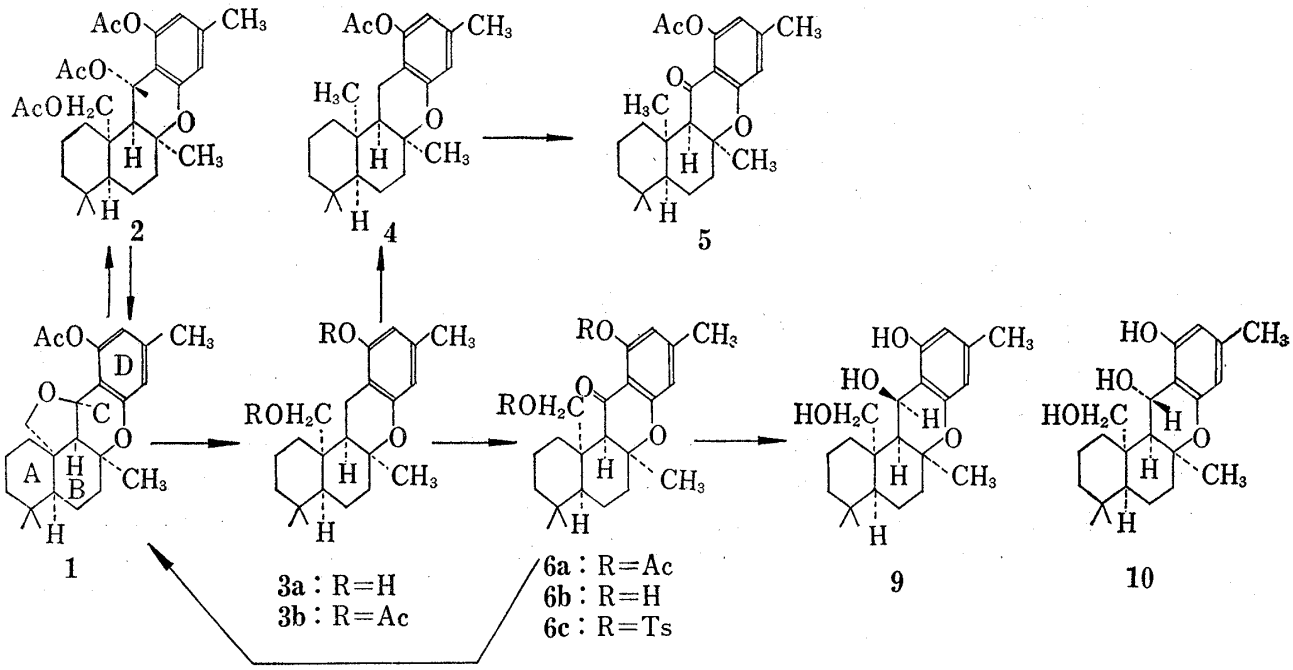

Chart 1

181.5°. The yield of **6a** was lower[6] as compared to the yield reported for the conversion of **4** into **5**.[2] Treatment of the ketodiacetate (**6a**) thus obtained with lithium aluminum hydride in ether reformed siccanin (**1**), but the yield of **1** was quite low. Chromatographic separation of the reduction product afforded a tetracyclic triol (**9**) as amorphous powder in a fair yield. The NMR absorption of **9** corresponding to the benzylic proton appears as doublet, $J=7$ Hz, at 5.69 ppm, indicating that this proton has presumably the α-configuration. This is based on the observation of Hirai, *et al.*[2,3] wherein the α-benzylic proton appeared as a doublet as shown in the case of siccanin (**1**) because of a dihedral angle of about 45° between the benzylic proton and its neighboring angular proton; while the β-benzylic proton in the triacetoxy compound (**2**) appeared as a singlet because of the corresponding angle of about 85°.

Formation of siccanin and the triol (**9**) in the reduction of **6a** might be explainable in the following way. Initially, reduction of **6a** afforded a mixture of triols, one with α-hydroxy group (**10**) and the other with β-hydroxy group (**9**) at the benzylic position. The former (**10**) would not be isolable, being easily converted into siccanin with reformation of a tetrahydrofuran ring in the same way as the siccanin formation from **2**. The relative ratio of siccanin and the triol (**9**) was found to be approximately 1:3 and shows that hydride attack preferentially occurs from the unhindered α-side with predominant formation of the triol (**9**). Based on this fact, attension was directed to methods for utilizing the major product (**9**) for reforming siccanin. A ditosylate (**6c**) of the tetracyclic ketodiol was expected to be a more suitable starting material; wherein a β-hydroxy group could attack the carbon atom of

6) As a by-product in this oxidation reaction, a lactone acetate (**7**) was isolated in a low yield. Saponification of **7** gave a lactone alcohol as crystals of mp 183—184°, whose infrared absorption due to the lactone function appeared at a low frequency at 1715 $cm^{-1}$and whose nuclear magnetic resonance (NMR) absorption due to angular methylene protons shifted to a lower field as an AB-pattern quartet centering at 3.77 ppm, indicating the presence of a 6-membered lactone like **8**. Formation of this lactone (**7**) is presumably due to an oxidative cleavage of the aromatic ring of **6a** during the oxidation reaction.

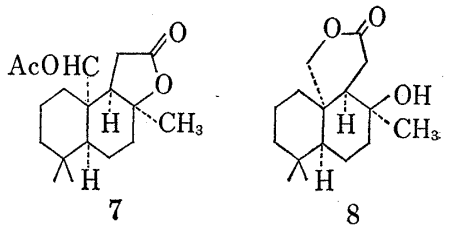

Chart 2

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the angular methylene group having tosyloxy leaving group to form siccanin in a better yield.

Saponification of the ketodiacetate (**6a**) afforded a syrupy ketodiol (**6b**) which was converted into a ditosylate (**6c**). Although **6c** was not prepared in a pure form, lithium aluminum hydride reduction of the crude product (**6c**) was carried out and siccanin (**1**) was obtained in a fairly good yield. Thus, the tetracyclic diol (**3a**) was shown to be an important key substance in synthesis of siccanin (**1**).

Some of these derivatives were tested biologically and it was found that the triol (**9**) exhibited one half activities against dermatophytes as compared to siccanin.

Before attempting the siccanin synthesis, the possibility of preparing a hexahydroxanthene skeleton corresponding to the B, C, and D rings of siccanin was investigated in the following way.

The condensation of 2,6-dimethoxy-4-methylbenzaldehyde[7] (**11**) and cyclohexanone was carried out in the presence of sodium methoxide; however, the resulting product was found to be mainly a bis-benzylidene compound (**12**), mp 195—205°, along with a small amount of the expected monobenzylidene compound (**13**), mp 121—123.5°. Using excess cyclohexanone in this reaction afforded a fair yield of **13**. On the other hand, following the method

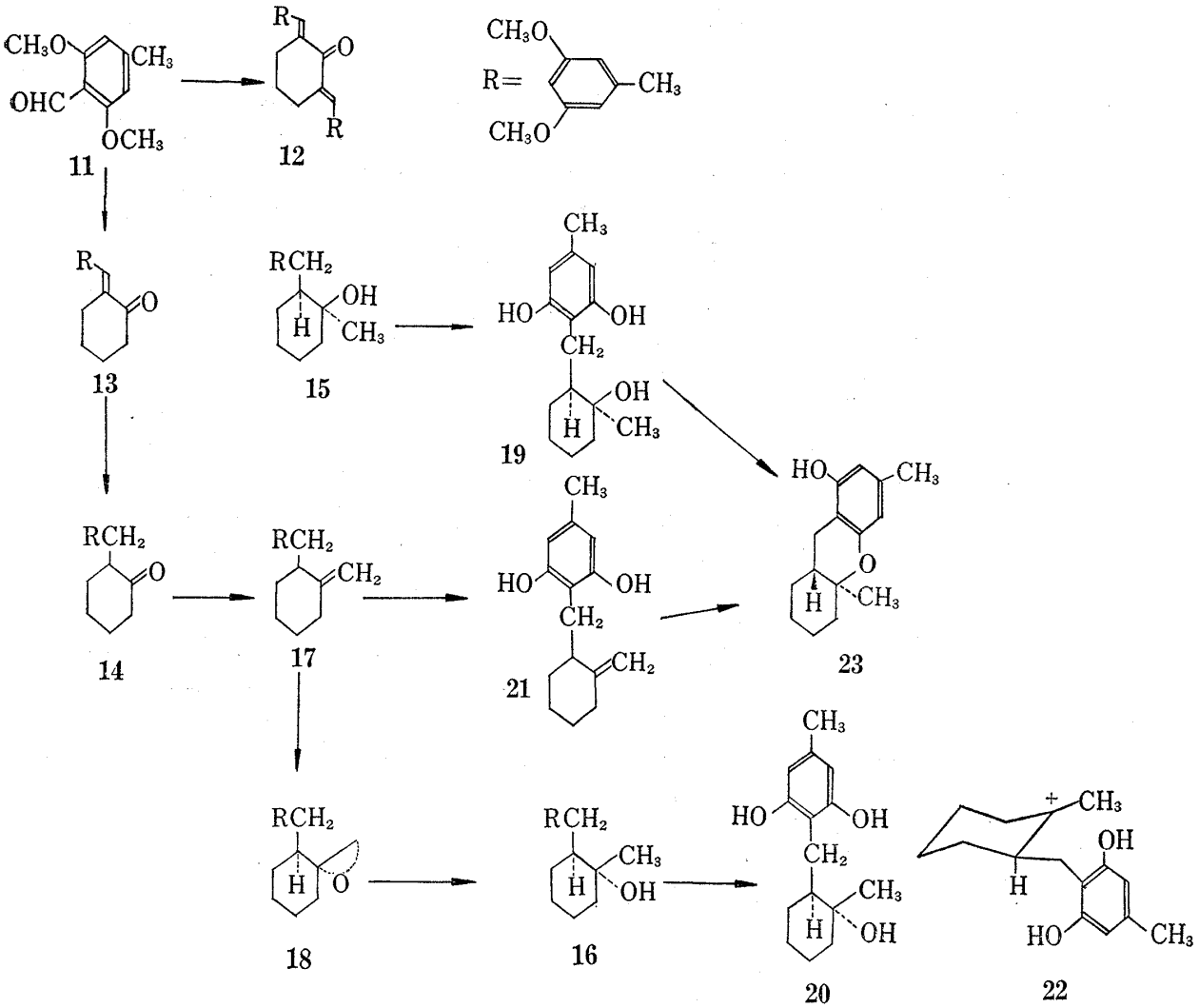

Chart 3

7) R. Adams and R.B. Carlin, *J. Am. Chem. Soc.*, **65**, 360 (1943).

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of Birkofer, *et al.*,[8] the condensation of **11** with cyclohexanone morpholinoenamine and successive treatment with acid gave the monobenzylidene compound (**13**) in a good yield. Hydrogenation of **13** over palladium-charcoal yielded a saturated ketone (**14**), mp 99—100.5°, whose treatment with methylmagnesium iodide afforded a tertiary alcohol (**15**), mp 65—69°. The tertiary alcohol (**15**) thus obtained was the main product, but was not prepared in a pure state and was contaminated[9] with a small amount of an possible isomeric alcohol (**16**) which will be described later.

On the other hand, treatment of the ketone (**14**) with triphenylmethylenephosphorane gave an exocyclic methylene compound (**17**), mp 86—87°, in a good yield. Epoxidation of **17** with *m*-chloroperbenzoic acid afforded mainly a crystalline epoxide (**18**), mp 100—102°, whose treatment with lithium aluminum hydride yielded the epimeric alcohol (**16**) as crystals, mp 134—136°. Based on these facts, presumably either the Grignard reaction of the ketone (**14**) affording the tertiary alcohol (**15**) or the epoxidation reaction of the methylene compound (**17**) proceeded with a fair degree of stereospecificity and the attack of these reagents was conducted from the unhindered α-side; consequently, the Grignard addition of **14** gave an α-methyl-β-hydroxy compound (**15**) and epoxidation of **17** also gave an α-epoxide (**18**); the epimeric alcohol (**16**) derived from **18** would have an α-hydroxy-β-methyl group.

Following the method of Mechoulam and Gaoni,[10] demethylation of these compounds was carried out; on treatment with methylmagnesium iodide at a high temperature, **15** was converted into a syrupy triol (**19**), **16** into a crystalline triol (**20**), mp 158—159.5°, and **17** into a methylene diol (**21**), mp 115.5—116°, respectively. These triol (**19**, **20**) and the diol (**21**) were found to be fairly unstable and in part afforded cyclized products during some stage in the chemical procedure after the demethylation reaction or during the chromatographic purification of the reaction products. Cyclization of these compounds into hexahydroxanthene compound was also easily conducted on treating with *p*-toluenesulfonic acid in boiling benzene. The NMR analysis showed that each reaction product obtained from **19**, **20**, or **21** involved almost the same composition of cyclized products. This suggests that this cyclization reaction does not consist of a concerted process but proceeds through a common carbonium ion like **22** no matter which alcohol is cyclized.

Thus, a hexahydroxanthene derivative (**23**), mp 121—122.5°, was isolated as the prominent product in this cyclization reaction. Unfortunately, there is no reliable physical data available for assessing the ring juncture of **23**; however, based on recently published observation of Mechoulam, *et al.*,[11] a *trans* juncture would be postulated for **23**. They studied analogous cyclizations in the course of hashish synthesis and reported that acid-catalysed cyclization of cannabigerol (**24**) predominantly results in formation of a *trans* hexahydroxanthene compound (**25**). Cyclization of an isomeric diene (**26**) mainly affords a *cis* isomer (**27**), suggesting that a corresponding possible intermediate (**28** or **29**) controls the ring juncture of the resulting cyclic product (**25** or **27**) with high stereospecificity; an equatorial side chain (**28**) results in the formation of the *trans* compound (**25**) and an *axial* side chain (**29**) the *cis* compound (**27**). In the case of the cyclization of **19**, **20**, or **21**, the bulky side chain in the carbonium ion intermediate (**22**) would be favorably located in the *equatorial* position similar to the case of cannabigerol (**28**), resulting in the preferential formation of the *trans* hexahydroxanthene compound (**23**). Further studies on the structure of **23** are now in progress.

The NMR spectrum of the byproduct mixture left from the isolation of **23** exhibited a singlet absorption at 1.12 ppm and also a doublet one centering at 0.83 ppm, J=6.5 Hz,

8) L. Birkofer, S.M. Kim, and H.D. Engls, *Chem. Ber.*, **95**, 1495 (1962).
9) This impurity was indicated by the appearance of a weak singlet at 1.31 ppm along with a main singlet absorption at 1.35 ppm due to protons of the newly-built methyl group in the NMR spectrum of **15**.
10) R. Mechoulam and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965).
11) R. Mechoulam and B. Yagen, *Tetrahedron Letters*, **1969**, 5349.

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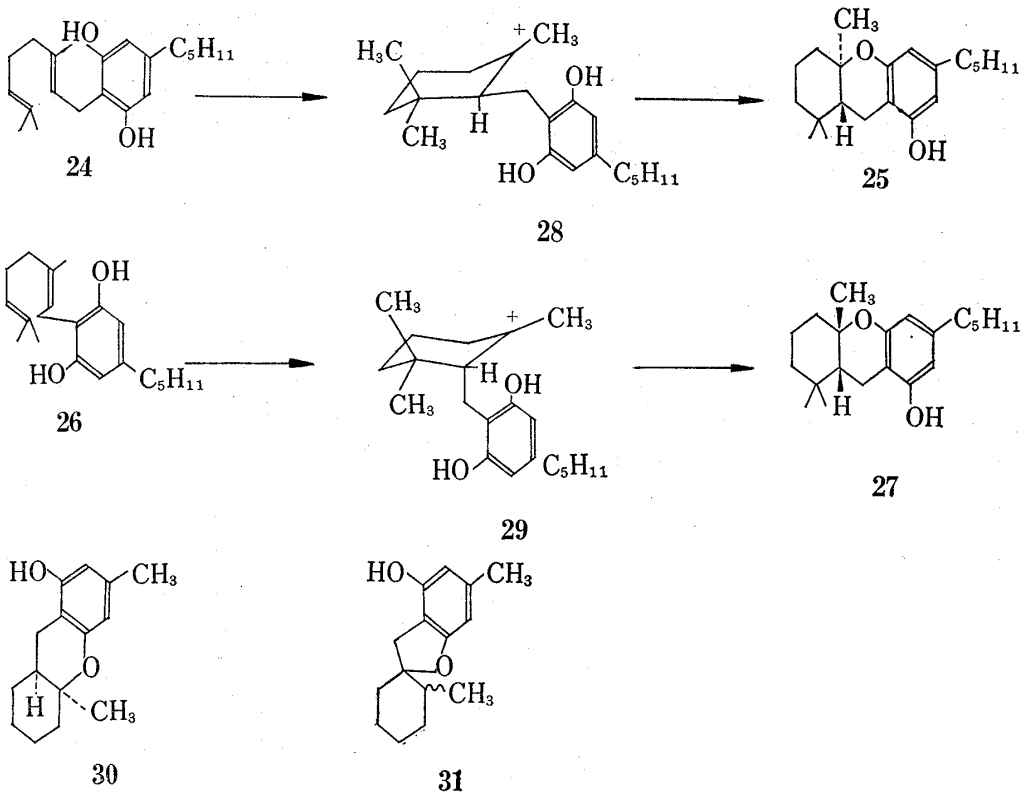

Chart 4

at a higher field, along with a singlet absorption at 1.18 ppm due to the main cyclic product (**23**). This indicates some contamination of isomeric cyclic compounds. The former singlet absorption may be due to a possible *cis* derivative (**30**) based on the reported data[11] that the methyl signal of the *cis* isomer (**27**) falls at a higher field as compared to the *trans* isomer (**25**). The latter doublet absorption may be ascribed to contamination by a spirodihydrobenzofuran type isomer (**31**) which might be formed *via* a hydride shift in the carbonium ion (**22**). Analysis and separation of this byproduct mixture by means of vapor phase chromatography were unsuccessful.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were determined on a Perkin–Elmer Model 221 or Perkin–Elmer Infracord, ultraviolet (UV) spectra on a Beckman Model DK-2, NMR spectra on a Varian A-60 spectrometer, and mass spectra on a JEOL JMS-OLSG spectrometer. Removal of solvent *in vacuo* was accomplished with a rotating flash evaporator at 20—30 mmHg and usually at 35—50°. Plates for thin-layer chromatography (TLC) were prepared with Silica Gel G (E. Merck AG) and visualization of spots was effected by spraying iodine or a solution of NH_4VO_3 in 50% H_2SO_4, followed by heating. Columns for ordinary chromatography were repared with Wako Gel Q-22 or Alumina II—III (E. Merck AG). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad; sh., shoulder.

Tetracyclic Diol Diacetate (3b)——Following the procedure of Hirai, *et al.*,[2] siccanin (**1**) was treated with $LiAlH_4$–$AlCl_3$ (1 : 2) complex[12] to give the tetracyclic diol (**3a**) as a syrup which was purified by chromatography on silica gel. On treatment with Ac_2O in pyridine in the usual manner, **3a** gave a diacetate (**3b**) as a syrup in a good yield. Analytical sample was obtained by chromatography on silica gel. IR ν_{max}^{Nujol} cm^{-1}: 1773, 1750, 1645, 1583, 1240. NMR ($CDCl_3$) δ ppm: 0.92 (3H, s), 1.04 (3H, s), 1.19 (3H, s), 2.10 (3H, s), 2.26 (3H, br. s), 2.29 (3H, s), *ca.* 2.6 (2H, m), 4.07 (1H, d, J=12.5 Hz), 4.44 (1H, d, J=12.5 Hz), 6.41 (1H, br. s), 6.50 (1H, br. s). *Anal.* Calcd. for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 73.07; H, 8.48.

Tetracyclic Ketodiacetate (6a)——To a stirred solution of 2.34 g of **3b** in 30 ml of AcOH was added 7.5 ml of 25% CrO_3 solution in 80% aqueous AcOH at 0° and the mixture was stirred at 0° for 37 hr. After

12) B.R. Brown and G.A. Sommerfield, *Proc. Chem. Soc.*, **1958**, 7.

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treating in the usual manner, 1.30 g of a syrupy crude product was obtained and chromatographed over 15 g of silica gel. Fractions eluted with benzene–ether (50:1, v/v) were evaporated and the residue was recrystallized from hexane–benzene, given 625 mg of **6a** as prisms, mp 175—179°. The analytical sample of **6a** was obtained by further recrystallization from the same solvent as prisms and dried at 100° under a reduced pressure, mp 178.5—181.5°. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1733, 1675, 1627, 1241. NMR ($CDCl_3$) δ ppm: 0.94 (3H, s), 1.03 (3H, s), 1.26 (3H, s), 2.11 (3H, s), 2.32 (3H, br. s), 2.34 (3H, s), 2.37 (1H, s), 3.97 (1H, d, J=12.5 Hz), 4.53 (1H, d, J=12.5 Hz), 6.43 (1H, br. s), 6.65 (1H, br. s). *Anal.* Calcd. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.33; H, 7.92.

Further elution with the same solvent mixture and evaporation of the solvent afforded 118 mg of a lactone acetate (**7**) as a syrup which exhibited a different behavior on TLC. IR $\nu_{max}^{liq.}$ cm^{-1}: 1775, 1743, 1239. NMR ($CDCl_3$) δ ppm: 1.00 (6H, s), 1.39 (3H, s), 2.09 (3H, s), 2.55—2.8 (2H, m), 3.87 (1H, d, J=12 Hz), 4.10 (1H, d, J=12 Hz).

The crude **7** thus obtained was saponified with base as follows. A solution of 110 mg of the crude **7**, 150 mg of KOH in 1 ml of 50% aqueous MeOH was warmed at 50° for 15 min and the cooled mixture was diluted with H_2O and washed with ether. The remaining aqueous layer was acidified with dil. HCl and extracted several times with ether. The combined ether extracts were dried and evaporated *in vacuo*, leaving 65 mg of crystals which were recrystallized from benzene–hexane to give 35 mg of a lactone alcohol (**8**) as needles, mp 180—181.5°. The analytical sample, mp 183—184°, was obtained by further recrystallization. IR ν_{max}^{Nujol} cm^{-1}: 3470, 1715. NMR ($CDCl_3$) δ ppm: 0.94 (3H, s), 1.05 (3H, s), 1.17 (3H, s), 2.55—2.85 (2H, m), 3.77 (1H, dd, J=11.2, 1.3 Hz), 5.00 (1H, d, J=11.2 Hz). *Anal.* Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.36; H, 10.56.

$LiAlH_4$ Reduction of Ketodiacetate (6a)——To a solution of 157 mg of **6a** in 4 ml of ether was added 100 mg of $LiAlH_4$ in one portion with cooling and stirring and the mixture was standing for 2 hr at room temperature with stirring. After decomposition of the excess reagent by careful addition successively of AcOEt and dil. HCl, the ether layer was collected and dried. Evaporation of the solvent from the ether layer left 101 mg of a syrup which was dissolved in 1 ml of benzene and the mixture was refluxed for 30 min. The cooled solution was charged on a silica gel column (2.5 g). Fractions eluted with benzene were evaporated and the residue was recrystallized from hexane, giving 21 mg of siccanin (**1**), mp 137—137.5°, which was identified with the authentic sample by IR and NMR spectrometry. Further elution with benzene–ether (4:1, v/v) and evaporation of the solvent gave 65 mg of a tetracyclic triol (**9**) as amorphous powder. IR ν_{max}^{Nujol} cm^{-1}: 3250 (br.), 1637, 1583. NMR ($CDCl_3$) δ ppm: 0.95 (3H, s), 1.21 (3H, s), 1.25 (3H, s), 2.21 (3H, s), 2.03 (1H, d, J=7 Hz), 3.80 (1H, d, J=12 Hz), 4.40 (1H, d, J=12 Hz), 5.69 (1H, d, J=7 Hz), 6.16 (1H, br. s), 6.25 (1H, br. s). *Anal.* Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.01; H, 8.95.

Tetracyclic Ketodiol (6b)——A mixture of 313 mg of **6a**, 200 mg of KOH, 1.5 ml of H_2O, 5 ml of dioxane, and 2 ml of MeOH was stirred for 2 hr at room temperature, then, was acidified by careful addition of dil. HCl and extracted with ether. The extract was washed with H_2O, dried and evaporated *in vacuo*, leaving 233 mg of a brown syrup which was chromatographed over 5 g of silica gel. Fractions eluted with benzene–ether (30:1, v/v) were evaporated to give 187 mg of **6b** as a syrup. IR ν_{max}^{Nujol} cm^{-1}: 3480, 1642, 1630 (sh.), 1572. NMR ($CDCl_3$) δ ppm: 0.97 (3H, s), 1.25 (3H, s), 1.29 (3H, s), 2.28 (3H, s), 2.74 (1H, s), 3.70 (1H, d, J=12 Hz), 4.11 (1H, d, J=12 Hz), 6.23 (1H, s), 6.28 (1H, s). *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 74.07; H, 8.60.

Conversion of Tetracyclic Ketodiol (6b) into Siccanin (1) through Ditosylate (6c)——To a solution of 60 mg of **6b** in 0.7 ml of pyridine was added 0.2 g of TsCl and the mixture was standing for 4 days at room temperature. After treating in a usual manner, the product was purified by chromatography on 2.5 g of silica gel. The purified ditosylate (**6c**) (85 mg) was dissolved in 3 ml of ether and 40 mg of $LiAlH_4$ was added in one portion at 0° with stirring. After stirring for 2 hr with cooling, the excess reagent was decomposed by careful addition of AcOEt. The mixture was diluted with H_2O and extracted with ether. The ether extract was dried, and evaporated *in vacuo* to give 57 mg of syrup which was purified by chromatography on 2.5 g of silica gel. Fractions eluted with benzene–hexane (1:4, v/v) were evaporated and the residue (34 mg) was recrystallized from hexane to afford 26 mg of siccanin (**1**), mp 137—137.5°, which was identified with an authentic sample.

2,6-Bis(2,6-dimethoxy-4-methylbenzylidene)cyclohexanone (12) and 2-(2,6-Dimethoxy-4-methylbenzylidene)-cyclohexanone (13)——i) To a $NaOCH_3$ solution prepared by dissolving 0.25 g of Na in 16 ml of MeOH was added 1.2 g of 2,6-dimethoxy-4-methyl-benzaldehyde[7] (**11**) and 1.6 g of cyclohexanone with cooling and stirring. The mixture stood at room temperature for 5 hr with stirring and was further warmed at 50° for 30 min. After standing at room temperature overnight, the resulting precipitates were collected and 0.92 g of a bis-benzylidene compound (**12**) was obtained as yellow needles, mp 195—205°. IR ν_{max}^{Nujol} cm^{-1}: 1662, 1610, 1580. NMR ($CDCl_3$) δ ppm: 2.36 (6H, s), 3.79 (6H, s), 3.81 (6H, s), 6.41 (4H, s), 7.68 (2H, br.). *Anal.* Calcd. for $C_{25}H_{30}O_5$: C, 73.14; H, 7.37. Found: C, 73.70; H, 7.20.

The filtrate left by collection of **12** was diluted with 20 ml of H_2O, neutralized with dil. HCl, and extracted with benzene. The extract was evaporated *in vacuo*, leaving 0.73 g of a crystalline mass which was recrystallized from MeOH to give 0.33 g of a monobenzylidene compound (**13**), mp 118—120°. Analytical sample was obtained by further recrystallization from the same solvent as needles, mp 121—123.5°.

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IR ν_{max}^{Nujol} cm^{-1}: 1670, 1613, 1594, 1575. NMR ($CDCl_3$) δ ppm: 2.36 (3H, s), 3.80 (6H, s), 6.38 (2H, s), 7.32 (1H, br.). *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.64; H, 7.78.

ii) A solution of 2 g of **11** and 2.5 g of N-(Δ^1-cyclohexenyl)morpholine in 5 ml of benzene was refluxed for 15 hr. The mixture was cooled and 20 ml of 2N dil. HCl was added. The stirred mixture was warmed for 1 hr on a steam bath and, after cooling, was extracted with benzene. The extract was washed with dil. aqueous $NaHCO_3$ and evaporated *in vacuo*, leaving 2.76 g of a syrup which was digested with MeOH to give 200 mg of **12**, mp 205°. After filtration of **12**, the filtrate was concentrated *in vacuo* and the residue was chromatographed over 40 g of alumina. The fractions eluted with benzene–hexane (7: 3, v/v) was evaporated and recrystallized from MeOH, giving 1.13 g of **13**, mp 122—123°. Further elution with benzene–ether (3: 2, v/v) followed by removal of the solvent and recrystallization of the residue from MeOH gave 144 mg of **12**.

2-(2,6-Dimethoxy-4-methylbenzyl)cyclohexanone (14)——A solution of 1.62 g of **13** in 70 ml of EtOH was hydrogenated over 200 mg of Pd-C (10%) for 2 hr. After the catalyst was filtered off, the mixture was evaporated *in vacuo* to dryness and the residue was recrystallized from MeOH, giving 1.19 g of **14** as prisms, mp 99—100.5°. Concentration of the mother liquor of the recrystallization gave a second crop of **14** (0.17 g), mp 94—97°. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1613, 1589. NMR ($CDCl_3$) δ ppm: 2.33 (3H, s), 3.77 (6H, s), 6.35 (2H, s). Mass Spectrum (75 eV) *m/e*: 262 (M^+). *Anal.* Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.98; H, 8.36.

1α-Methyl-2β-(2,6-dimethoxy-3-methylbenzyl)cyclohexanol-1 (15)——To a cooled solution of 1.18 g of **14** in 15 ml of tetrahydrofuran was added 5 ml of 3M MeMgI etheral solution dropwise with stirring and the mixture was stirred for 2 hr. Then, the mixture was carefully diluted with H_2O, saturated with NH_4Cl (solid), and extracted with benzene. The extract was evaporated *in vacuo*, leaving 1.28 g of a syrup which crystallized on digestion in cold hexane. The crystals were collected and 0.91 g of **15**, mp 65—69°, were obtained. IR ν_{max}^{Nujol} cm^{-1}: 3490, 1610, 1588. NMR ($CDCl_3$) δ ppm: 1.24 (3H, s), 2.33 (3H, s), 3.81 (6H, s), 6.37 (2H, s); (C_6D_6) δ ppm: 1.31, 1.35 (3H, each s, *ca.* 1:10), 2.24 (3H, s), 3.45 (6H, s), 6.28 (2H, s). *Anal.* Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.09; H, 9.36.

1-Methylene-2-(2,6-dimethoxy-4-methylbenzyl)cyclohexane (17)——To a cooled and stirred solution prepared by dissolving 180 mg of 50% NaH mineral oil suspension (after washing twice with hexane) in 2 ml of dimethylsulfoxide at 70° was added dropwise a solution of 1.29 g of triphenylmethylphosphonium bromide in 3.7 ml of dimethylsulfoxide under N_2 atmosphere and the mixture was stirred with cooling for 20 min. To the resultant solution was added 325 mg of **14** at room temperature with stirring and, then, the mixture was kept at room temperature for 15 min. After cooling, the mixture was diluted with cold water and extracted with ether. The extract was washed with H_2O, dried and evaporated *in vacuo*. Recrystallization of the residue from EtOH gave 261 mg (80%) of **17** as leaflets, mp 86—87°. IR ν_{max}^{Nujol} cm^{-1}: 3080, 1643, 1611, 1590, 884. NMR ($CDCl_3$) δ ppm: 2.32 (3H, s), 2.77 (2H, d, J=7.5 Hz), 3.75 (6H, s), 4.61 (2H, br. s), 6.35) 2H, s). *Anal.* Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.06; H, 9.37.

Epoxide (18)——To an ice-cold solution of 786 mg of **17** in 7 ml of dichloromethane was added dropwise a solution of 700 mg of *m*-chloroperbenzoic acid in 7 ml of dichloromethane during a period of 15 min with stirring and, then, the mixture was stirred at 0° for 1 hr. A further solution of 200 mg of peracid in 3 ml of dichloromethane was added to the stirred mixture and stirring maintained for 30 min at 0°. After the mixture was successively washed with aqueous Na_2CO_3 and with H_2O, the organic layer was collected and dried. After evaporation of the solvent, the residue was chromatographed over 15 g of silica gel. Fractions eluted with hexane–benzene (1: 2, v/v) were evaporated, recovering 30 mg of **17**, mp 80—83°. Fractions eluted with benzene were evaporated and the residue was recrystallized from hexane, giving 408 mg of **18**, mp 99—102°. Analytical sample was obtained as prisms, mp 100—102°, by further recrystallization from hexane. IR ν_{max}^{Nujol} cm^{-1}: 1605, 1588, 1138, 813. NMR ($CDCl_3$) δ: ppm 2.32 (3H, s), 3.75 (6H, s), 6.33 (2H, s). *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.85; H, 8.76.

1β-Methyl-2β-(2,6-dimethoxy-4-methylbenzyl)cyclohexanol (16)——To a solution of 304 mg of **18** in 12 ml of tetrahydrofuran was added portionwise 40 mg of $LiAlH_4$ with stirring and cooling and the mixture was refluxed for 20 min with stirring. After decomposition of the excess reagent by careful addition of H_2O, the mixture was extracted with ether several times. The combined ether extracts were washed with H_2O and dried. The residue obtained by evaporation of the solvent was recrystallized from hexane to give 244 mg of **16**, mp 127—134°. An analytical sample was obtained as needles, mp 134—136°, from benzene–hexane. IR ν_{max}^{Nujol} cm^{-1}: 3480, 1590, 1120, 972, 815. NMR (C_6D_6) δ ppm: 1.31 (3H, s), 2.23 (3H, s), 3.43 (6H, s), 6.27 (2H, s). *Anal.* Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.15; H, 9.51.

1-Methylene-2-(2,6-dihydroxy-4-methylbenzyl)cyclohexane (21)——A mixture of 292 mg of **17** and 5 ml of etheral 3M MeMgI was gradually heated under evaporation of the solvent and the mixture was kept at 160—165° for 2 hr. After cooling, the mixture was carefully decomposed by addition of H_2O, then saturated with NH_4Cl (solid) and extracted with ether. The extract was dried and evaporated to dryness *in vacuo*, leaving 233 mg of a syrup which partly crystallized on standing. Recrystallization from benzene–hexane afforded 37 mg of **21** as leaflets, mp 112—114.5°. The mother liquor of the recrystallization was concentrated and chromatographed over 6 g of silica gel. Fractions eluted with benzene–ether (5:1, v/v) were evaporated *in vacuo*, and recrystallization of the residue from benzene–hexane afforded 89 mg of **21** as

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needles, mp 114—115.5°. An analytical sample was prepared by further recrystallization from the same solvent and melted at 115.5—116°. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3350, 3075, 1641, 1590, 885. NMR ($CDCl_3$) δ ppm: 2.21 (3H, s), 4.71 (4H, s, CH_2=C- and 2-OH), 6.23 (2H, s). *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.95.

3,10a-Dimethyl-5,6,7,8,8a,10a-hexahydroxanthen-1-ol (23)——A solution of 50 mg of **21** and 1 mg of TsOH in 2 ml of benzene was refluxed for 1 hr. After cooling, the mixture was washed with H_2O, dried, and evaporated *in vacuo*. The residue was chromatographed on 2 g of silica gel and fractions eluted with benzene–hexane (5:1, v/v) were evaporated, giving 45 mg of the cyclization product as a syrup which crystallized partly on standing. The collected crystals were recrystallized from benzene–hexane, giving 15 mg of **23** as prisms, mp 121—122.5°. IR ν_{max}^{Nujol} cm^{-1}: 3380, 1627, 1590, 1050, 817. NMR ($CDCl_3$) δ ppm: 1.18 (3H, s), 2.19 (3H, s), 4.98 (1H, br. s, OH), 6.17 (1H, br. s). *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.50; H, 8.72.

1α-Methyl-2β-(2,6-dihydroxy-4-methylbenzyl)cyclohexanol (19) and Its Cyclization Reaction——As described in the case of the formation of **21**, 318 mg of **15** was treated with 5 ml of 3M MeMgI at 155—160° for 1 hr, yielding 292 mg of a syrup whose TLC chromatogram revealed contamination by a small amount of **15**. The mass spectrum of this syrup showed M^+ 250, indicating that the main component is demethylated product. The crude **19** thereby obtained was chromatographed over 7 g of silica gel. Fractions eluted with benzene and benzene–ether (20:1, v/v) were evaporated, giving 143 mg of a mixture of the cyclization products including **23**. Fractions eluted with benzene–ether (3:1, v/v) afforded 123 mg of the pure **19** as a syrup after evaporation of the solvent. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400 (br.), 1635, 1591. NMR ($CDCl_3$) δ ppm: 1.26 (3H, s), 2.19 (3H, s), 6.25 (2H, s).

The sample of **19** did not furnish a satisfactory analytical data. Treatment of 160 mg of **19** with TsOH in benzene gave the same reaction product as obtained from treatment of **21**, which was indicated by NMR analysis.

1β-Methyl-2β-(2,6-dihydroxy-4-methylbenzyl)cyclohexanol (20) and Its Cyclization Reaction——As described above in the case of the formation of **23** treatment of 150 mg of **16** with 3 ml of 3M MeMgI etheral solution afforded 117 mg of a crude triol which was recrystallized from benzene, giving 45 mg of **20** as needles, mp 156—158°. Further, a second crop of **20** (13 mg) was obtained from the recrystallization mother liquor on standing. Analytical sample was obtained as needles, mp 158—159.5°, by further recrystallization from benzene. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3220, 1600, 1106, 826. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.07; H, 9.09.

Treatment of 103 mg of **20** with TsOH in benzene gave the same reaction product as obtained from treatment of **21**, which was indicated by NMR analysis.

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