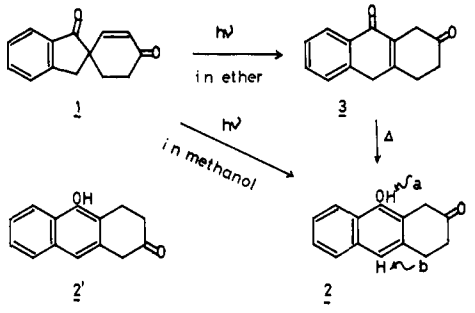
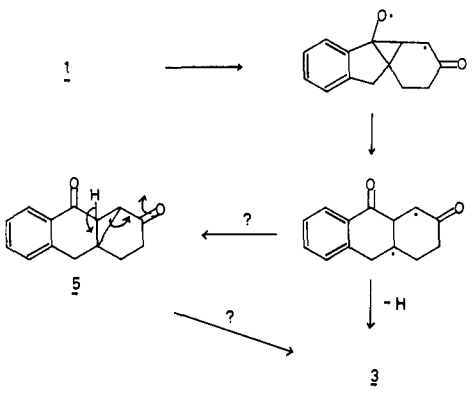
Scheme I



Scheme II



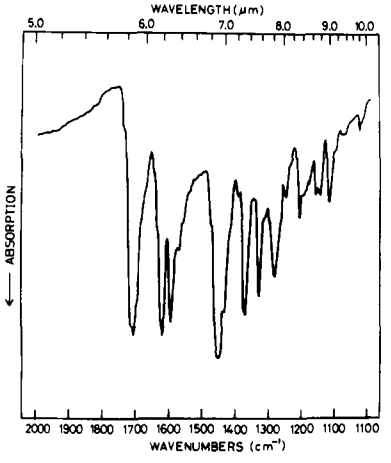


Figure 1. Infrared absorption spectra (25 °C, Nujol) of **3**.

cm^{-1} (see Figure 1); ^1H NMR ($CDCl_3$) 2.40–3.00 (m, 4 H), 3.35 (s, 2 H), 3.77 (s, 2 H), 7.23–7.70 (m, 3 H), 8.20 ppm(m, 1 H);[9] ^{13}C NMR ($CDCl_3$) 208.6, 183.7, 150.9, 139.5, 132.1, 131.3, 130.4, 127.8, 127.2, 126.5, 37.4, 37.2, 35.0, and 30.8 ppm;[9] UV λ_{max} ($CHCl_3$) 253 (log ϵ, 4.10), 268 (4.05), 300 nm (sh). The thermal rearrangement of **3** to **2** was observed during triturating with ethanol or dimethyl-d_6 sulfoxide (Me_2SO).[6] From these results **3** was assigned as 3,4-dihydro-2,9(1*H*,10*H*)-anthracenedione. This is the first example of the photochemical preparation of the ketone tautomer of a naphthol. A plausible mechanism for the photoisomerization from **1** to **3** is shown in Scheme II. This may be an example of the oxa-di-π-methane rearrangement of β,γ-enones.[10]

Acknowledgment. We thank S. Kohara and M. Honjo for some preliminary studies.

(10) (a) We are indebted to the referees for a suggestion about the mechanism. (b) Houk, K. N. *Chem. Rev.* **1976**, *76*, 1. Schuster In "Rearrangements of Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Chapter 17. Domb, S.; Bozzato, G.; Saboz, J. A.; Schaffner, K. *Helv. Chim. Acta* **1969**, *52*, 2436.

Total Synthesis of Racemic Siccanin

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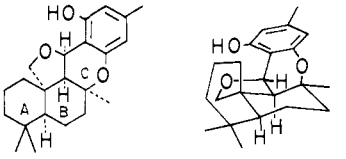
Siccanin (**1**) is a mold metabolite isolated from the culture broth of *Helminthosporium siccans*[1] and exhibits a remarkable antifungal activity against a variety of fungi, in particular, *Trichophyton interdigitale* and *T. asteroids*, that cause fungal infection in skin.[2] This compound is clinically utilized thereby.



1a **1b**

Since its unique structure involving the unusual cis-, syn-, cis-fused A/B/C ring system was revealed as **1b** in 1967 by X-ray crystallographic study,[3] some synthetic approaches to this intriguing target were reported.[4]

Siccanin is regarded as a drimane sesquiterpene combined with orcinol. Herein is described the first total synthesis of racemic siccanin by a novel approach. The synthesis is divided into three major tasks: (a) stereoselective synthesis of *cis*-octalone **10**, (b) development of **10** to the formyldecalol **17** with the drimane structure, (c) subsequent elaboration to the tetracyclic hydrofuran derivative **24**, and acid treatment of **24** to lead to siccanin methyl ether (**26**) (see Schemes I and II).

The known, readily available keto ester **2**[5] was submitted to the Robinson annulation ($MeCOCH{=}CH_2$, NaOMe, MeOH) to yield octalone **3**, mp 121–122 °C (Scheme I). The octalone was smoothly methylated (MeI, *t*-BuOK, *t*-BuOH) to give liquid dimethyl ketone **4**. Reduction of the hindered ketone carbonyl of **4** to methylene group was achieved by reduction [$NaB(CN)H_3$, *p*-TsOH, sulfolane, DMF, 100 °C][6] of its tosylhydrazone **5** ($TsNHNH_2$, MeOH), mp 217 °C (decomp), affording octalin **6**, mp 43–44 °C. Reduction of **6** ($LiAlH_4$, DME) to alcohol **7**, mp 38–40 °C, and methylation (MeI, NaH, DME) of the resulting hydroxy group gave methyl ether **8**, mp 52–54 °C. Acetal exchange reaction of **8** (*p*-TsOH, acetone, 25 °C) gave oily deconjugated octalone **9**.

After a number of attempts for isomerization of **9** to conjugated enone **10**, it was eventually found that treatment of the former with *p*-toluenesulfonic acid (0.5 equiv) in methanol at 50 °C yielded an equilibrium mixture consisting of the ketone **9** and **10** in a 1:4 ratio. The oily enone **10** separated by silica gel chromatography was shown to be a *cis*-octalone as mentioned below, and no formation of its trans isomer was observed.

Unambiguous assignment of the cis stereochemistry was done by transformation of the decalone **18**, quantitatively obtained by hydrogenation of **10** (H_2, 10% Pd-C, EtOH), into the known trimethyl ketone **19**[7] as follows: replacement of the methoxy group

(1) Ishibashi, K. *J. Antibiot., Ser. A* **1962**, *15*, 161.
(2) Ishibashi, K.; Hirai, K.; Arai, M.; Sugasawa, S.; Endo, A.; Yasumura, A.; Masuda, H.; Muramatsu, T. *Ann. Sankyo Res. Lab.* **1970**, *22*, 1.
(3) (a) Hirai, K.; Nozoe, S.; Tsuda, K. Itaka, Y.; Shirasawa, M. *Tetrahedron Lett.* **1967**, 2177. (b) Hirai, K.; Suzuki, K. T.; Nozoe, S. *Tetrahedron* **1971**, *27*, 6057.
(4) Nozoe, S.; Hirai, K. *Tetrahedron* **1971**, *27*, 6073. Oida, S.; Ohashi, Y.; Yoshida, A.; Ohki, E. *Chem. Pharm. Bull.* **1972**, *20*, 2634. Yoshida, A.; Oida, S.; Ohashi, Y.; Tamura, C.; Ohki, E. *Ibid.* **1972**, *20*, 2642. Oida, S.; Ohashi, Y.; Ohki, E. *Ibid.*, **1973**, *21*, 528.
(5) Rukes, R. M.; Poos, G. I.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 1401.
(6) Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 1793. Lane, C. F. *Synthesis* **1975**, 135.
(7) Ohloff, G.; Näf, F.; Decorzant, R.; Thommen, W.; Sundt, E. *Helv. Chim. Acta* **1973**, *56*, 1414.

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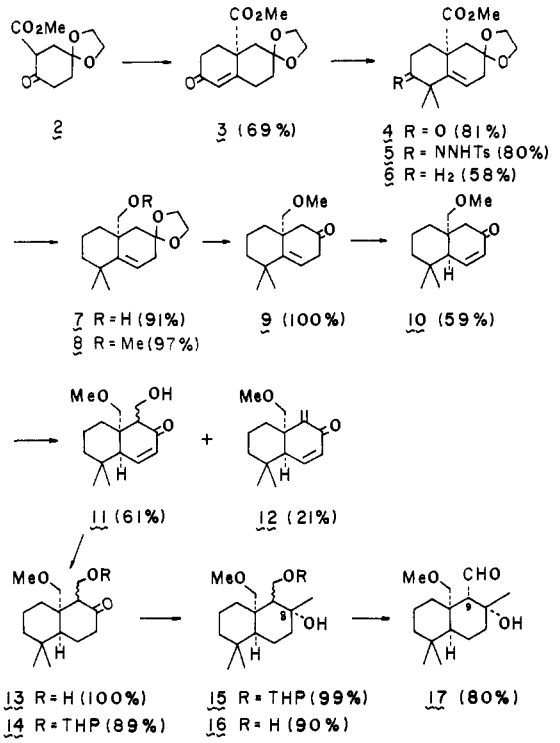
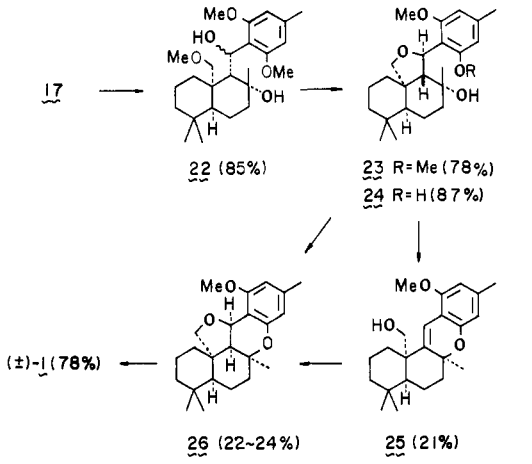
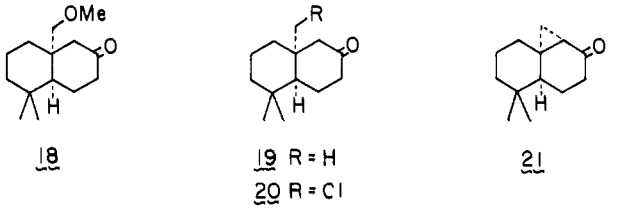
Scheme I



Scheme II



of **18** by chlorine (gaseous HCl, $ZnCl_2$, Et_2O) led to chloro ketone **20** in 73% yield, whose transformation into cyclopropyl ketone



21 cleanly proceeded by deprotonation with sodium hydride (THF, 74% yield). Reductive cleavage of the cyclopropane ring (Li, liquid NH_3) afforded **19** in 58% yield, which was identified with an authentic sample by spectral comparison.

Construction of the expected intermediate, formyldecalol **17**, started with the regioselective hydroxymethylation of the enolate of **10** [$(i\text{-Pr})_2NLi$, DME, −78 °C] with gaseous formaldehyde, the reaction yielding oily hydroxy ketone **11**[8] along with methylene ketone **12**, mp 97–98 °C. Hydrogenation of **11** (H_2, 10% Pd–C, EtOH) to **13**, followed by protection of the hydroxy group [DHP, pyridinium *p*-toluenesulfonate (PPTS),[9] CH_2Cl_2], gave tetrahydropyranyl ether **14**, which was then methylated (excess MeLi, Et_2O) to produce oily carbinol **15**.[10] After hydrolysis (PPTS, moist EtOH, 60 °C), the resulting diol **16** was oxidized (PCC, CH_2Cl_2)[11] to **17**,[10] mp 102–104 °C.

Introduction of the aromatic ring was carried out by the condensation of the aldehyde **17** with lithiated orcinol dimethyl ether[12] (DME, from −75 to 0 °C), and diol **22**, mp 152–153 °C, was obtained as a mixture with a minor quantity of its epimer with respect to the benzylic hydroxy group (Scheme II).

Tetrahydrofuran ring formation by generation of carbonium ion arising from elimination of the benzylic hydroxy group of **22** followed by intramolecular attack of the oxygen atom in the angular methoxymethyl group was effectively performed by treatment of the epimer mixture of **22** with 1 equiv of pyridinium chloride[13] (CH_2Cl_2, 25 °C, 30 min), which led to the tetracyclic compound **23**, mp 167–167.5 °C, whose X-ray crystallographic analysis definitely established the stereostructure as shown in **23**.[14] Subsequent partial demethylation (NaSEt, DMF, 100 °C) furnished monophenol **24**, mp 185–186 °C.

In anticipation of formation of C(8)–C(9) tetrasubstituted double bond by dehydration of **24** and successive olefin–phenol cyclization, the final elaboration to siccanin (**1**) was carried out by acid treatment. While concentrated sulfuric acid treatment (*n*-$PrNO_2$, 25 °C) resulted in formation of siccanochromene E methyl ether (**25**),[15,16] mp 144–145 °C, Lewis acid catalyzed reaction of **24** ($BF_3{\cdot}OEt_2$, CH_2Cl_2, 25 °C, or $SnCl_4$, PhH, 25 °C) proceeded to give siccanin methyl ether (**26**),[3b] mp 134–135 °C albeit in low yield. Treatment of **25** under the same reaction conditions also afforded **26** in a similar yield.

Demethylation of **26** (NaSEt, DMF, 100 °C) produced racemic siccanin, mp 154–155 °C, which was indistinguishable from the natural specimen in TLC, IR, NMR, and MS spectra.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (354,187). We are grateful to Dr. G. Ohloff for the spectrum of trimethyl ketone **19**, Professor S. Nozoe for the spectrum and a sample of authentic siccanochromene E methyl ether, and Sankyo Co. Ltd. for a generous gift of natural siccanin. We also thank Dr. C. Kabuto for the X-ray analysis.

Supplementary Material Available: Spectroscopic data for compounds **3–18** and **20–24** (5 pages). Ordering information is given on any current masthead page.

(8) The stereochemistry of the hydroxymethyl group has been unclarified because of uncertain predominant conformation of the *cis*-octalone system.

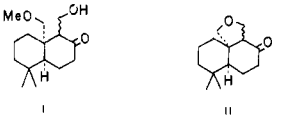
(9) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(10) The depicted stereochemistry at C(8) [and C(9) in **17**] in this compound was concluded from the stereochemistry of **23** which was unambigously assigned.

(11) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1978**, 2647.

(12) Adams, R.; Wolff, H.; Cain, C. K.; Clark, J. H. *J. Am. Chem. Soc.* **1940**, *62*, 1770.

(13) In the course of this study, we experienced similar neighboring group participation in the reaction of i with *p*-toluenesulfonyl chloride in pyridine, which gave tetrahydrofuran derivative ii in high yield. This results prompted us to employ pyridinium chloride in this reaction.



(14) Detailed result will be published in due course.

(15) Nozoe, S.; Suzuki, K. T. *Tetrahedron* **1971**, *27*, 6063.

(16) Judging from the fact that siccanin methyl ether (**26**) was recovered unchanged under the same reaction conditions, **25** would be derived through a sequence of reactions: (1) dehydration of **24** to a tetrasubstituted olefin and (2) protonation to the reactive ether function, followed by concurrent carbon–oxygen bond cleavage in the tetrahydrofuran ring and chromene ring formation (see formula iii).