Acknowledgment. We wish to thank Emeritus Professor S. Yamada and Professor K. Koga of University of Tokyo for their interests and discussions.

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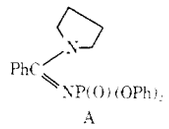
(8) According to substrates and reaction conditions, 1,3-dipolar elimination products such as A from triazoline intermediates **3** were sometimes isolated, though in poor yields.



A

(9) All new compounds were fully characterized by NMR and IR spectral means and elemental composition. Known compounds were identified by comparing their physical data (melting or boiling points, IR and NMR spectra) with reported ones.
(10) In the one-flask procedure, the condensation reaction of a ketone **1** with pyrrolidine was carried out as described in the text, and the reaction solvent was removed in vacuo. Tetrahydrofuran was added to the residual crude enamine **2** under argon atmosphere, followed by the addition of DPPA. The reaction and workup were conducted as described in the typical procedure of the text.
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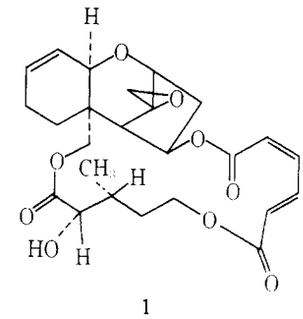
Received March 14, 1978

Synthetic Strategy toward Verrucarins. An Approach toward Verrucarol

Summary: The synthesis of a key tetrahydrochromanone intermediate toward a sesquiterpene portion of the verrucarins, potent antitumor agents, involves novel utilization of cyclobutanone annulation, a new approach to creation of α,β-unsaturated-γ-hydroxylated esters, and a new rearrangement.

Sir: The synthesis of the verrucarins such as verrucarin A (**1**), a class of potent antitumor agents, requires consideration of the sesquiterpene portion (cf. verrucarol, **2**) and the attendant macrocycle.[1,2] We wish to report a new approach toward verrucarol which (a) employs cyclopropyl phenyl sulfide to create most of the carbon skeleton except for the cyclohexyl ring, (b) develops a new approach to γ-hydroxylation, and (c)



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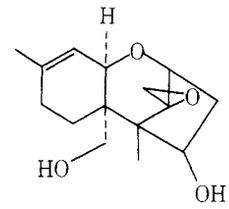

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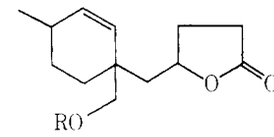


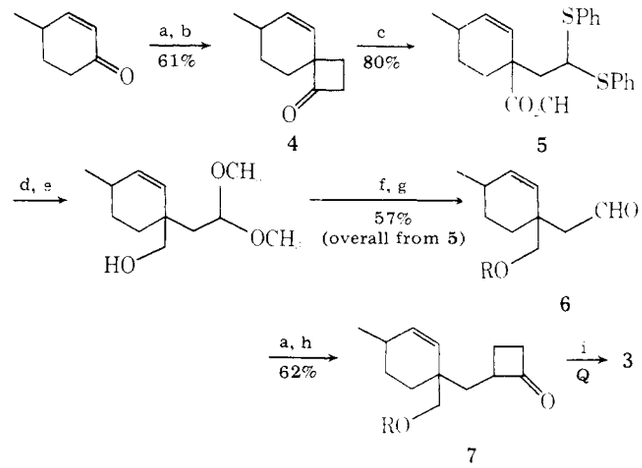
3

illustrates a novel arearrangement to create the tetrahydrochromanone ring system.

Scheme I outlines the synthesis of the key lactone **3**, which contains all of the carbon atoms of **2** save two (methyl group and epoxide methylene). [3.5]Spiroannulation of 4-methylcyclohex-2-en-1-one utilizing 1-lithiocyclopropyl phenyl sulfide[3,4] gave the desired cyclobutanone **4**[5] as a mixture of two stereoisomeric adducts (ratio ~1:1). Since this stereochemistry is immaterial with respect to the overall synthesis, no attempt was made to separate the isomers. Secosulfenylation[6] gave the desired ring-cleaved compound **5** in which the geminal carbon was fully elaborated in a functionally differentiated way. Transacetalization, reduction, O-methylation or benzoylation, and hydrolysis prepared the substrate for the final lactone annulation. Cyclobutanone annulation to **7** (R = CH_3 or benzoate)[5] proceeded as before, except that *p*-toluenesulfonic acid in refluxing moist benzene effected the rearrangement of the intermediate cyclopropyl carbinol.[7] Basic hydrogen peroxide[8] completed the synthesis of **3** (R = CH_3 or benzoate).[5] In this case, creation of the lactone via the Baeyer–Villiger oxidation takes advantage of the chemospecificity imparted by the strain of the cyclobutyl ring.

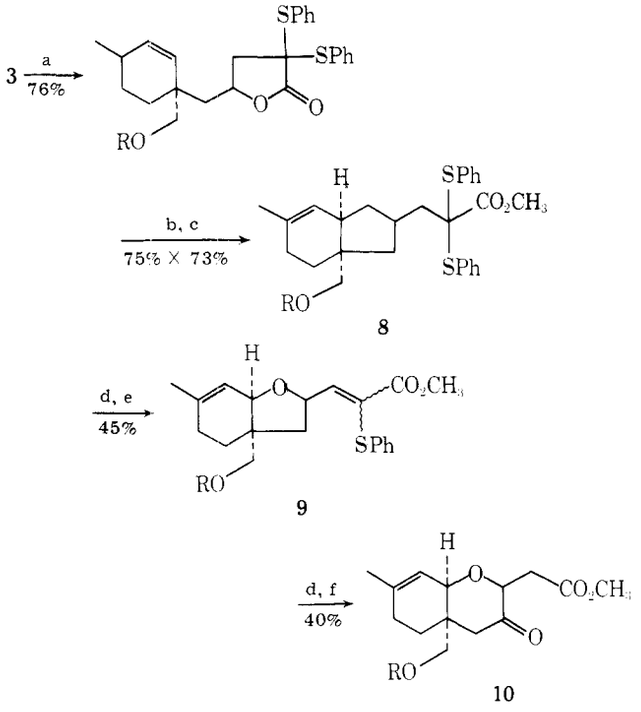
With the completion of the main parts of the carbon skeleton, attention focused upon the adjustment of the oxidation

Scheme I. Synthesis of Lactone 3



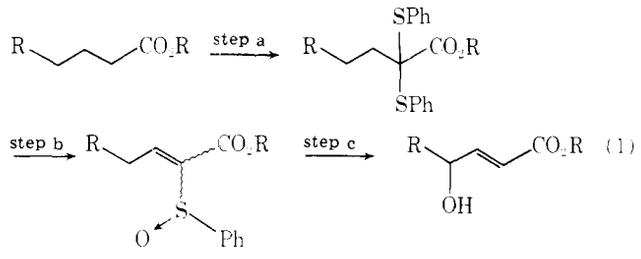
(a) c-$CH_2CH_2C(Li)(SPh)$, THF, 0 °C. (b) HBF_4, H_2O, ether, room temp. (c) $NaOCH_3$, PhSSPh, CH_3OH, reflux. (d) I_2, CH_3OH, reflux. (e) $LiAlH_4$, ether, reflux. (f) NaH, DME, CH_3I or PhCOCl. (g) HCl, H_2O, THF room temp. (h) TsOH, PhH, H_2O, reflux (i) NaOH, H_2O_2, 0 °C.

Scheme II. Preparation of Tetrahydrochromanone



(a) LDA, $PhSSO_2Ph$, THF, −78 → −35 °C. (b) CuBr, $PhCO_3C(CH_3)_3$, PhH, reflux. (c) NaOH, THF H_2O then HCl, H_2O, then CH_2N_2, ether. (d) MCPBA, CH_2Cl_2, −15 °C. (e) CH_2Cl_2, $(CH_3O)_3P$, 46 °C. (f) CH_3OH, DBU, reflux.

level. Initially, the lactone ring was prepared for elaboration of the chromanone by the development of a procedure for the creation of a γ-hydroxyl-α,β-unsaturated system as illustrated in eq 1.[9] The key bissulfenylation (step a)[10] creates the ap-

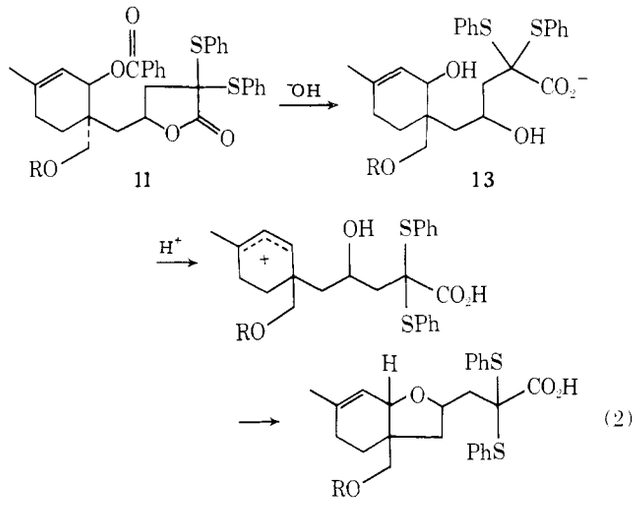


(1)

propriate oxidation level in which it is rearranged by a combination of sulfoxide elimination (step b)[10] and [2,3]sigmatropic rearrangement of allyl sulfoxides (step c).[11]

Bissulfenylation (see Scheme II) proceeded smoothly (step a of eq 1). Before completion of steps b and c, the allylic oxidation of the cyclohexene was carried out. *tert*-Butyl perbenzoate in the presence of cuprous salts[12] avoided oxidation at sulfur and gave high regiochemical control to **11** (see eq 2) as determined by the presence of the vinyl methyl group (δ 1.65), a methine proton (δ 4.5) adjacent to the benzoate, and one vinyl proton (δ 6.15). This compound was normally directly hydrolyzed and acidified, in which case the tetrahydrofuran **8**[5] was isolated. The critical formation of **8** establishes the requisite cis ring juncture for the verrucarol system. The origin of **8** presumably results from solvolysis of the sensitive alcohol **13** and subsequent internal trapping during the acidification, as shown in eq 2. Such internal trappings are known to give high specificity for the cis ring juncture.[13] Thus, the use of the [6.5] ring system rather than the [6.6] one provides the stereochemical control of the ring juncture.

Oxidation and thermolysis of the sulfoxide[10] proceeds

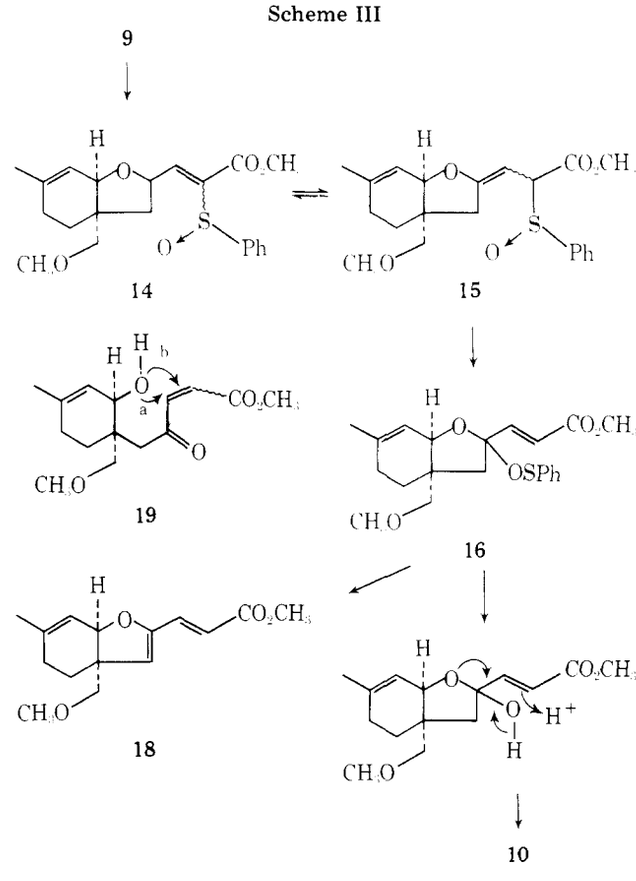


(2)

smoothly to the α-sulfenylated-α,β-unsaturated system **9** (step b of eq 1), which is then oxidized to the corresponding sulfoxide (Scheme III). Base establishes the equilibrium between the vinyl and allyl sulfoxides (**14** ⇄ **15**), in which the latter can suffer [2,3]sigmatropic rearrangement to **16** and in situ desulfenylation to **17**. Isomerization of **17** to **10** involves expansion of a five-membered ring to a six and conversion of a C=C to a C=O; thus, this transformation should be strongly exothermic. Indeed, under these conditions **17** is not isolated but only **10**[5] is observed. Performing this reaction in the absence of a sulfenic ester trap (PhH, $(C_2H_5)_3N$, reflux), only the dihydrofuran **18**,[5] which presumably results from elimination of benzenesulfinic acid in **16**, is observed and is completely homogeneous.

It is tempting to speculate that the rearrangement of **17** to **10** is concerted as represented by the arrows in **17**. Oxygen migrations to electron-deficient carbon are well precedented[14]

Scheme III



as well as embodied in the concept of neighboring group participation of ethereal oxygens in the formation of carbonium ions. Alternatively, **17** would open to **19**, which has the option of reclosing to a six- (path a) or seven-membered ring (path b). The former represents a 6-exo trig (favored) and the latter a 7-endo trig (disfavored) cyclization,[15] which also leads to the expectation of formation of **10**. The tetrahydrochromanone **10** is a mixture of the two epimers at C(2) which could easily be separated. Raphael has worked out a procedure to convert such systems to the trichothecane skeleton of the verrucarols.[2c] Thus, the synthesis of **10** represents the formal completion of the first stage of the verrucarin problem. Work is currently underway to develop alternative approaches to these later stages as well as develop methodology for the macrocyclic ring.

Acknowledgment. We wish to thank the National Institutes of Health (National Cancer Institute) for their generous support of our program.

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(5) **4**: IR 1785, 1649 cm^{-1}; NMR δ 0.93 and 0.95 (two d, J = 8 Hz, total 3 H), 2.93 (pt, J = 8 Hz, 2 H), 5.46 (ps, 2 H). **5**: IR 1730, 1575, 1475 cm^{-1}; NMR δ 0.75 and 0.85 (two d, J = 7 Hz, total 3 H), 2.15 (two d, J = 6 Hz, total 12 H), 3.55 (two s, total 3 H), 4.1 and 4.25 (two t, J = 6 Hz, total 1 H), 5.55 (m 2 H). **7** (R = CH_3): IR 1775 cm^{-1}; NMR δ 0.95 (d, J = 8 Hz, 3 H), 2.9 (pt, J = 8 Hz, 2 H), 3.05 (s, 2 H), 3.25 (s, 3 H), 5.45 (AB, J = 8 Hz, 2 H). **3** (R = CH_3): IR 1770 cm^{-1}; NMR δ 0.95 (d, J = 8 Hz, 3 H), 3.25 (s, 3 H), 5.5 (m, 2 H). **8** (R = CH_3): IR 1740 cm^{-1}; NMR δ 1.7 (two s, total 3 H), 2.9 and 3.1 (AB, J = 10 Hz, 2 H), 3.15 (two s, total 3 H), 3.2 (s, 3 H), 4.3 (m, 1 H), 5.2 (ps, 1 H). **10** (isomer A): IR 1730 cm^{-1}; NMR (270-MHz proton) δ 1.7 (s, 3 H), 2.1 and 2.2 (AB, J = 16 Hz, 2 H), 2.3 (dd, J = 16, 5 Hz, 1 H), 2.6 (dd, J = 16, 5 Hz, 1 H), 3.1 and 3.3 (AB, J = 8 Hz, 2 H), 3.3 (s, 3 H), 3.6 (s, 3 H). **10** (isomer B): IR 1730 cm^{-1}; NMR δ 1.7 (s, 3 H), 1.8 (ps, 2 H), 2.9 and 3.1 (AB, J = 8 Hz, 2 H), 3.2 (s, 3 H), 3.6 (s, 3 H), 3.8 (d, J = 5 Hz, 1 H), 4.0 (dd, J = 5 Hz, 1 H), 5.4 (d, J = 5 Hz, 1 H).
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Received March 28, 1978