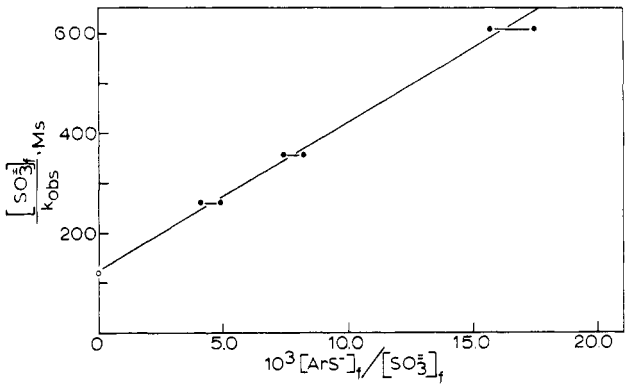

Figure 1. Nucleophilic substitution of II by sulfite ion in the presence and absence of added anion of 4-thiopyridone (ArS^-). Plot of the reciprocal of the apparent second-order rate constant vs. the ratio of 4-thiopyridone anion to sulfite ion concentrations. Horizontal bars indicate the contribution from substrate of ArS^- leaving group at 50 and 100% conversions. The open circle reflects the true second-order rate constant obtained in the absence of added ArS^-. The least-squares lines through the 50 and 100% points give slope to intercept ratios of 260 and 236, respectively. This ratio for the indicated line is 250.

outcome is not unprecedented: our first report on the substitution of thiamin contains such a contrast for azide and sulfite ions.[1] A similar "inversion" in rate and equilibrium constant ratios is found for an alkenethiolate ion and sulfite ion reacting with protonated quinazoline.[7]

As a check on the value of the rate constant ratio (Figure 1), competition experiments were performed using substrate IV to generate intermediate III. This material which has nicotinamide as a leaving group reacts ~280 times faster with sulfite ion than II.[8] Therefore IV may be converted into a mixture of II and sulfonic acid product in the presence of 4-thiopyridone and sulfite ion.[9] The product ratio was determined at 270 nm (pH 8.6, 25 °C) at three different concentrations of the two nucleophiles. A plot of the product ratio vs. the ratio of concentrations of the nucleophiles, corrected for the fraction present as reactive anion, is linear with a slope of 240. The remarkably good agreement between the rate constant ratios obtained from the two different types of experiments provides strong support for our analysis.[10]

Our results have considerable significance regarding the mechanism of nucleophilic substitution of thiamin and its analogues by thiaminase I.[11,12] In view of our demonstrations that substrates as diverse as I and II react by the common pathway given in Scheme I, we suggest that such a route may be followed by the enzymic reactions as well. Moreover, this pathway is reminiscent of that suggested for thymidylate synthetase.[13,14]

Acknowledgment. Our work was kindly supported by Grant AM-17442 from the National Institute of Arthritis, Metabolism and Digestive Diseases.

Supplementary Material Available: A listing of rate equations, a description of the competition experiments, and results (5 pages) is available. Ordering information is given on any current masthead page.

References and Notes

(1) Zoltewicz, J. A.; Kauffman, G. M. *J. Am. Chem. Soc.* **1977**, *99*, 3134.
(2) Intermediate III may also be written as a sultone.
(3) Zoltewicz, J. A. *Synthesis*, in press.
(4) At low substrate concentrations and when large amounts of thiolate ion are present initially, pseudo-first-order plots are linear over at least 4 half-lives. Under intermediate conditions such plots show pronounced curvature in the beginning and then become almost linear. This approximately linear region (>50% conversion) was used to obtain the rate constant for the second run in Table I.
(5) The total absorbance change for the last three kinetic runs is essentially the same, after correcting for small variations in the concentration of II. This indicates that (a) substitution goes to completion and not to an equilibrium condition and (b) II and 4-thiopyridone do not react in the absence of sulfite ion.
(6) The rate expression associated with Scheme I can be integrated exactly. To fit concentration–time data to this equation, a correct value for the competition constant is required. Our value obtained from Figure 1 allows us to obtain linear kinetic plots. Moreover, the slope is the second-order rate constant in the absence of inhibition. It has a value which is not significantly different from that given by the first entry in Table I.
(7) Cho, M. J.; Pitman, I. H. *J. Am. Chem. Soc.* **1974**, *96*, 1843.
(8) Unpublished result of G. M. Kauffman.
(9) This conversion into II is effected in 64% isolated yield on a preparative scale.
(10) The competition constant has, in general, two limiting forms, i.e., k_{-2}/k_3 and $k_{-1}k_{-2}/k_2k_3$. A future publication will discuss these possibilities.
(11) Evans, W. C. *Vitamins Hormones* **1975**, *33*, 467.
(12) Lienhard, G. *Biochemistry* **1970**, *9*, 3011.
(13) Pogolotti, A. L.; Santi, D. V. *Bioorg. Chem.* **1977**, *1*, 277.

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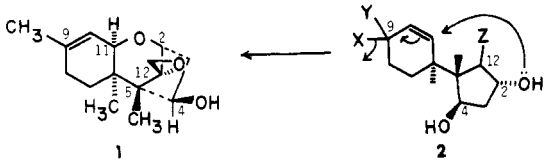
Total Synthesis of (±)-Trichodermol

Sir:

Trichodermol is a central member of the trichothecane group of terpenoid antibiotics and has been the subject of numerous synthetic investigations since its structure was revealed as **1** in 1964.[1] Although a total synthesis was reported in 1971 by Raphael and co-workers,[2] the failure of a certain key aldol cyclization to establish the C-4–C-5 bond in >10% yield made it clear that further work on trichothecane synthesis should be undertaken. The work that we describe here uses a different type of construction in which a preformed cyclopentanol (e.g., in **2**) cyclizes biomimetically along lines described previously[3] to produce the desired tricyclic system (see Scheme I). The synthetic problem thus effectively reduces to one in which a way must be found to relate the stereochemistry between the two isolated rings. As we will show, a cycloaddition–fragmentation sequence provides a mechanism for the desired stereocontrol and yields a novel pathway to (±)-trichodermol.

Our plan for the construction of an intermediate equivalent to **2** begins by the Diels–Alder addition of quinone to the cyclohexadienyl silyl ether **3**[4] (1 M in C_6H_6; 25 °C; 5 days). The highly crystalline adduct **4** (mp 73–73.5 °C) was readily obtained in 90% yield (Scheme II). Subsequent epoxidation (*t*-BuOOH, Triton B, THF; −20 °C; 82% yield) and Herz–Favorskii ring contraction[5] (NaOH, EtOH; 25 °C; 70% yield) proceeded regiospecifically to give the crystalline cyclopentenonecarboxylic ester **5** (mp 74.5–75.5 °C; IR (Nujol) 1720 cm^{-1}).[6] At this point, the C-4 hydroxyl was introduced stereospecifically by epoxidation (*t*-BuOOH, Triton B, THF; 25 °C; 92% yield) and dissolving metal reduction (Li, NH_3, EtOH, THF; 93% yield). The resulting triol (**6**, mp 116–117 °C) was monoacetylated (Ac_2O, C_5H_5N; 0 °C) and reduced photochemically[7] (deoxygenated HMPA, H_2O; 450-W medium-pressure Hanovia, quartz; 60–70% yield at 70% conversion) to the corresponding diol (**7**, mp 90–93 °C, NMR ($CDCl_3$) δ 1.10 (s, 3 H) and 1.12 (s, 3 H)). Although the less-hindered C-2 hydroxyl could not be directly derivatized for fragmentation, an alternative sequence ((1) PhCOCl,

Scheme I



1 **2**

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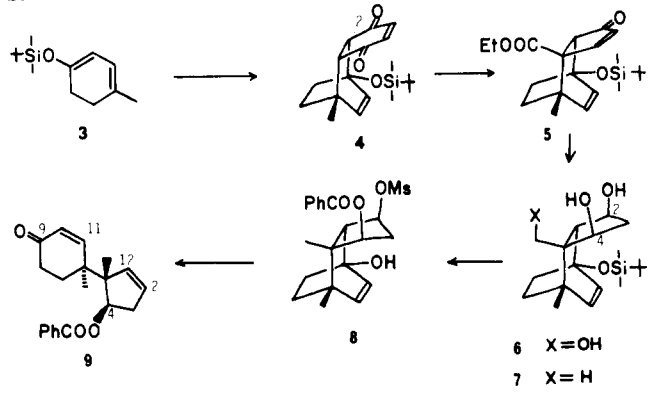
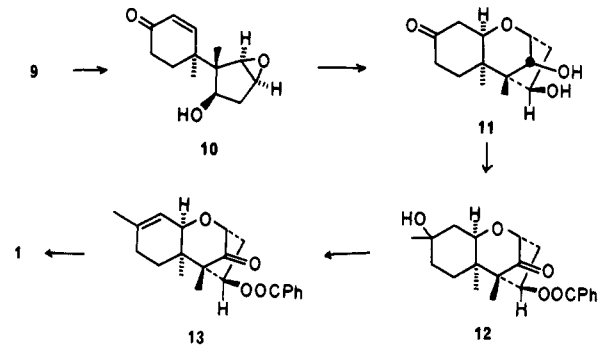
Scheme II



Scheme III



C_5H_5N; (2) Bu_4NF, THF; (3) K_2CO_3, MeOH; and (4) MsCl, Et_3N, CH_2Cl_2) gave the desired hydroxy mesylate (**8**, mp 164–165 °C) in >85% overall yield. Anionic fragmentation then proceeded cleanly by deprotonation with sodium hydride (THF; 0 °C) to yield **9** (IR (Nujol) 1680, 1715 cm^{-1}; 80% yield).

With the relative stereochemistry in the two isolated rings now fixed, we began to add the required functionality at C-2, C-9, and C-12. The most crucial of the operations involved trans hydroxylation of the C-2–C-12 olefin in such a way that the newly added hydroxyl at C-2 would have the α configuration as required for subsequent cyclization. While we anticipated that the bulk of the C-5 α substituent would direct both steps of an epoxidation–hydrolysis sequence to give the desired stereochemistry, the C-2–C-12 double bond of **9** was relatively unreactive with peracids[8] and it was necessary to deprotect C-4 temporarily prior to epoxidation. Thus debenzoylation (K_2CO_3, MeOH) preceded a hydroxyl-directed epoxidation (t-BuOOH, $VO(acac)_2$, CH_2Cl_2) and produced the β-oxide **10** (mp 103–104 °C) in 75% yield at 80% conversion. Acid-catalyzed glycol formation was somewhat sluggish but proceeded (2% aqueous H_2SO_4, CH_3COCH_3; 45 °C) to give the expected inversion at C-2 as shown in Scheme III by direct formation of the bridged tricyclic intermediate **11**[9] (mp 150–151 °C; 60% yield).

Final elaboration to trichodermol (**1**) was carried out straightforwardly. Thus methylation at C-9 (MeLi, THF; 80% yield), monobenzoylation at C-4 (PhCOCl, C_5H_5N; 0 °C; 86% yield) and oxidation at C-12 ($CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2; 88% yield) gave **12** (mp 148–150 °C) which underwent regioselective dehydration ($POCl_3$, C_5H_5N; 60% yield) to give a 7:1 mixture of olefins. The major isomer **13** (mp 180–182 °C) was isolated by chromatography on silica gel and was converted into **1** as described previously for the corresponding acetate[2] ((1) $Ph_3P{=}CH_2$, THF; (2) MCPBA, CH_2Cl_2). The racemic trichodermol thus produced (mp 123.5–125 °C (lit.[2] 124–125 °C)) was indistinguishable by TLC, IR, NMR, and MS from a sample of natural trichodermol kindly provided by Professor B. B. Jarvis of the University of Maryland.[10]

References and Notes

(1) S. Abrahamsson and B. Nilsson, *Proc. Chem. Soc.*, 188 (1964).
(2) E. W. Colvin, S. Malchenko, R. A. Raphael, and J. S. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1989 (1973). See also S. C. Welch and R. Y. Wong, *Synth. Commun.*, **2**, 291 (1972); S. C. Welch and R. Y. Wong, *Tetrahedron Lett.*, 1853 (1972); D. J. Goldsmith, A. J. Lewis, and W. C. Still, *ibid.*, 4807 (1973); Y. Fugimoto, S. Yokura, T. Nakamura, T. Morikawa, and T. Tatsuno, *ibid.*, 2523 (1974); E. W. Colvin, S. Malchenko, R. A. Raphael and J. S. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 658 (1978); B. B. Snider and S. G. Amin, *Synth. Commun.*, **8**, 117 (1978).
(3) Y. Machida and S. Nozoe, *Tetrahedron*, **28**, 5113 (1972). In vitro model cyclizations: N. Masuoka, T. Kamikawa and T. Kubota, *Chem. Lett.*, 751 (1974); N. Masuoka and T. Kamikawa, *Tetrahedron Lett.*, 1691 (1976).
(4) Dienol silyl ether 3 was prepared by silylation of the kinetic enolate of 4-methylcyclohex-3-en-1-one ((a) $LiNiPr_2$, THF–HMPA; (b) t-$BuMe_2SiCl$); cf. G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **42**, 1015 (1977).
(5) Cf. W. Herz, V. S. Iyer, and M. G. Nair, *J. Org. Chem.*, **40**, 3519 (1975).
(6) We were unable to find more than traces of the other Favorskii product by a careful examination of the crude product and believe that the observed regioselectivity results from silyl oxygen-assisted σ overlap with the C-2 carbonyl.
(7) J.-P. Pete, C. Portella, C. Monneret, J.-C. Florent, and Q. Khuong-Huu, *Synthesis*, 774 (1977).
(8) Extended reaction of **9** with MCPBA gave competitive Baeyer–Villiger oxidation of the appended cyclohexenone.
(9) The bridged structure **11** was distinguished from an analogous fused one (conceivably formed from the alternative C-2, C-12 glycol) by the NMR of the derived diacetate: NMR ($CDCl_3$) δ 3.70 (m, $w/2$ = 10 Hz, 1 H, H-11), 4.29 (dd, J = 2, 5 Hz, 1 H, H-2), 5.30 (br d, J = 2 Hz, 1 H, H-12), 5.41 (dd, J = 4, 8 Hz, 1 H, H-4). Irradiation at δ 4.29 caused the tight doublet at 5.30 to collapse to a singlet.

(10) This work was supported by NIH Grant 5 R01 CA23094.
(11) Alfred P. Sloan Fellow, 1978–1980.

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Electronic Spectra of Model Oxy, Carboxy P450, and Carboxy Heme Complexes

Sir:

The optical spectra of the carboxy complex of reduced cytochrome P450 has been the subject of considerable experimental investigation.[1-3] In contrast to carboxyhemoglobin[2] and myoglobin,[4] the Soret band is split into two components with maxima at λ 363 and 450 nm, the latter giving the name to this class of heme proteins which are mixed function oxidases. The spectroscopic behavior of the dioxygen complex of these enzymes, which is part of their normal enzymatic cycle, is more ambiguous. However, two studies[5,6] of the intact complex reveal a split Soret with broadened and blue-shifted components at λ 340 and 420 nm. Model oxy[7] and carboxy[8-10] heme complexes with thiolate or mercaptide ligands appear to have very similar optical spectra to the intact proteins, with more uncertainty in the oxy complex.

To understand the origin of differences in their spectroscopic behavior, we have calculated the electronic spectra of model oxy and carboxy P450 complexes together with a model carboxy heme complex using a newly developed INDO method including transition metal complexes and extensive configuration interaction.[11-13] This program, with spectroscopic parameterization, has been used by us to successfully describe the ground state of model oxy and carboxy P450 complexes[14] and model oxy hemoglobin complexes,[15] accounting for the quadrupole splitting in Mössbauer resonance of these complexes. It has also been used to successfully describe the ground state and/or spectral properties of $(FeCl_4)^-$, $(CoCl_4)^{2-}$, $(CuCl_4)^{2-}$,[13] and ferrocene.[16]

The geometry used for the six-coordinated ferrous P450 is based on an X-ray crystal structure of the porphyrin ring and the mercaptide (SCH_3–) and CO and O_2 axial ligands in model compounds.[17] The same geometry was used for the model

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