$$Fe^{II}P + CO \xrightarrow{k^{CO}} Fe^{II}P(CO) \qquad (1a)$$

which process would tend to augment the degree of net heme reduction. With the fully T-state hybrid[4d] under 1 atm of CO, CO binding is monophasic, $k^{CO} = 10^2\ s^{-1}$,[5] and the presence of CO does not significantly increase the extent of heme reduction subsequent to ^{3}ZnP formation. This indicates that $k_e > k^{CO}$, namely, $k_e > 10^2\ s^{-1}$. Such experiments performed with partially R-state tetramer,[4d] for which $k^{CO} = 5 \times 10^4\ s^{-1}$,[15] also show no increase in reduction. Although the response of multiple protein forms make analysis difficult, the observations suggest that the lower bound to k_e may well be 10-fold higher: $k_e > 10^3\ s^{-1}$. In any event, this result for k_e strongly suggests that rapid electron transfer within protein redox complexes such as that of cytochrome *c* and cytochrome *c* peroxidase, in which the heme edge-to-edge separation is thought to be 16 Å, need not involve complicated electron relay mechanisms.[6] Reaction 2 is less exothermic than reaction 1 yet is faster. Perhaps the latter process or both are in the "anomalous" regime, in which increasing the exothermicity actually reduces transfer rates because of the difficulty in dissipating the energy released.[2]

Measurements of temperature dependences, currently in progress, will allow us to separate tunneling from thermally activated contributions to both k_t and k_e; ligation of the ferriheme can be employed to change its redox potential, spin state, and, more generally, the nature of the Franck–Condon overlap between oxidized and reduced heme states.[16] Because these hybrids provide electron-transfer partners of known geometries, it is distinctly possible that the rates will be amenable to detailed analysis with current electron-transfer theories.

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Registry No. ZnP, 15442-64-5; heme, 14875-96-8; CO, 630-08-0.

(15) For further discussions of CO binding to these hybrids, see ref 4b.
(16) We have already observed that k_t varies with ligation of the ferriheme.

Total Synthesis of the Trichothecene Mycotoxin Anguidine

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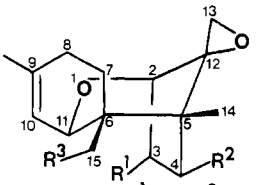
The trichothecene mycotoxins have been the focus of considerable interest due to the wide variety of biological activities they exhibit depending on the respective functional groups present on their unique tricyclic skeleton.[1] A variety of synthetic studies of trichothecenes have been reported.[2] Our interest in elucidating structure–activity relationships for this important group of sesquiterpenes led us to develop an enantioselective total synthesis of anguidine (**1**), which we report herein.[3] We chose to follow



	R^1	R^2	R^3
anguidine (1)	OH	OAc	OAc
trichodermol (2)	H	OH	H
verrucarol (3)	H	OH	OH

a scheme for assembling the trichothecene skeleton involving the addition of an A-ring unit to a fully functionalized C-ring unit, followed by an intramolecular cyclization providing the B-ring and thus completing the tricyclic skeleton.

Our synthesis originates with an asymmetric microbial reduction of 2-allyl-2-methyl-1,3-cyclopentanedione by actively fermenting bakers' yeast (*Saccharomyces cerevisiae*), which effects a stereoselective reduction of one of the two enantiotopic homomorphic carbonyl groups to provide the chiral starting material (2*S*,3*S*)-2-allyl-3-hydroxy-2-methylcyclopentanone, which was further elaborated to the fully functionalized C-ring precursor **4**.[4,5] With a fully functionalized C-ring precursor available, we next addressed the task of stereoselectively introducing the A-ring unit (see Scheme I). Our plan called for a Robinson annelation sequence on the hydroxymethylene **6**. We assumed that this bicyclo[3.2.1] system would add methyl vinyl ketone in a preferred exo manner similar to the model system reported by Roush.[6] The preparation of **6** was achieved by heating **4** with neat tris(dimethylamino)methane,[7] followed by mild acidic hydrolysis of the enamine **5**. The Michael reaction of **6** with methyl vinyl ketone proceeded as expected with exclusive exo addition providing the desired adduct **7**. An intramolecular aldol condensation was accomplished by treating **7** with lithium diisopropylamide at −78 °C and followed by elimination of the corresponding mesylates to give the enone **8**.[8] The A-ring unit was completed by treating **8** with methyllithium at −78 °C to provide the allylic alcohol **9**.[9]

Reduction of the A + C ring unit **9** with lithium aluminum hydride to give the tetraol **10** set the stage for an interesting study of possible intramolecular acid-catalyzed rearrangements. Inspection of molecular models indicated four possible modes of tetrahydropyran (B ring) formation by hydroxyl quenching of an intermediate allylic carbocation. Conformational analysis of these possibilities indicated that unfavorable interactions were minimized in a rearrangement that leads to the trichothecene skeleton. Experimental results of acid-catalyzed rearrangements of similar systems supported this prediction.[10] Treatment of the tetraol **10** with *p*-toluenesulfonic acid in dichloromethane gave a mixture of the desired trichothecene **11** and the unexpected [2.2.2]allyl ether **13**, resulting from cyclization of the C15 hydroxyl group in varying ratios depending on the reaction conditions.[11] Extended

(1) Reviews: (a) Tamm, C *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. (b) Bamberg, J. R.; Strong, F. M. In "Microbial Toxins"; Kadis, S., Ed.; Academic Press: New York, 1973; Vol. 3, pp 207–292. (c) Doyle, T. W.; Bradner, W. T. In "Anticancer Agents Based on Natural Product Models"; Cassidy, J. M., Douros, J., Eds.; Academic Press: New York, 1980; Chapter 2. Isolation and structure of anguidine: (d) Dawkins, A. W. *J. Chem. Soc. C* **1966**, 116.

(2) Several total synthesis of trichothecenes have been reported: (a) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989. (b) Still, W. C.; Tasi, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. (c) Schlessinger, R. H.; Nugent, R. A. *Ibid.* **1982**, *104*, 1116. (d) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *Ibid.* **1982**, *104*, 1114. (e) Trost, B. M.; McDougal, P. G. *Ibid.* **1982**, *104*, 6110. (f) Roush, W. R.; D'Ambra, T. E. *Ibid.* **1983**, *105*, 1058. Other pertinent synthetic studies are referenced in the above reports.

(3) Early portions of this work were presented at the 25th Congress, International Union of Pure and Applied Chemistry, Vancouver, B. C., Canada, Aug 1981. The work described in this communication was presented at the 185th American Chemical Society National Meeting, Seattle, WA, Mar 1983.

(4) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820.

(5) Brooks, D. W.; Grothaus, P. G.; Palmer, J. T. *Tetrahedron Lett.* **1982**, *23*, 4187.

(6) Roush, W. R.; D'Ambra, T. E. *J. Org. Chem.* **1980**, *45*, 3927.

(7) Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976**, *4459*.

(8) Attempts to effect the aldol condensation under equilibrating conditions resulted in a retro-Michael reaction to give **6**.

(9) Only one isomer seemed to be produced as indicated by ^{1}H NMR, but the assignment of stereochemistry is tentative.

(10) Refer to the results reported in ref 2c,f.

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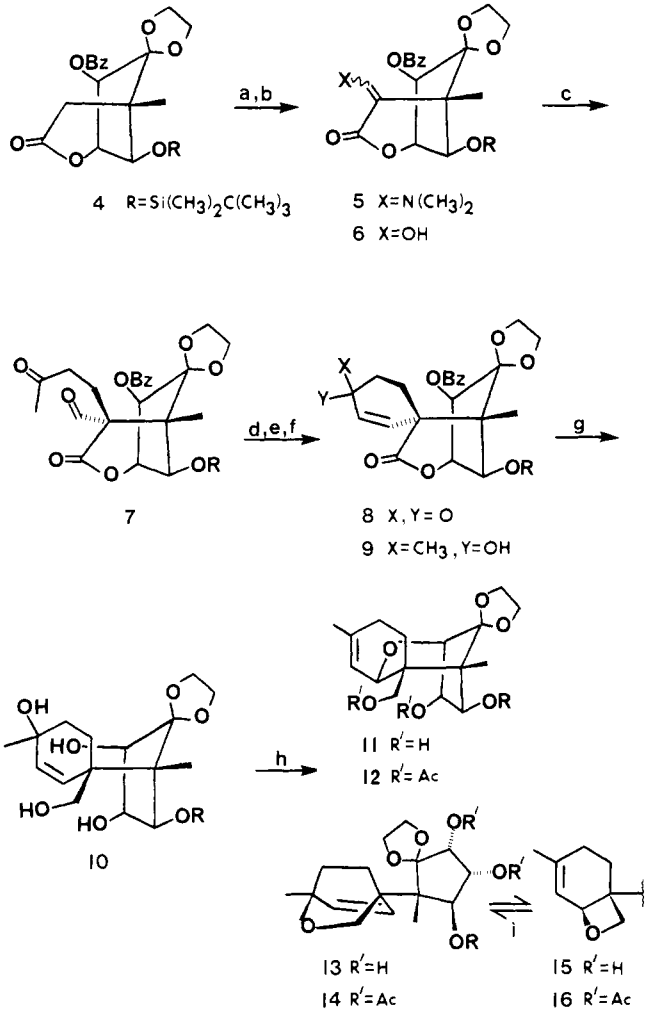
Scheme I

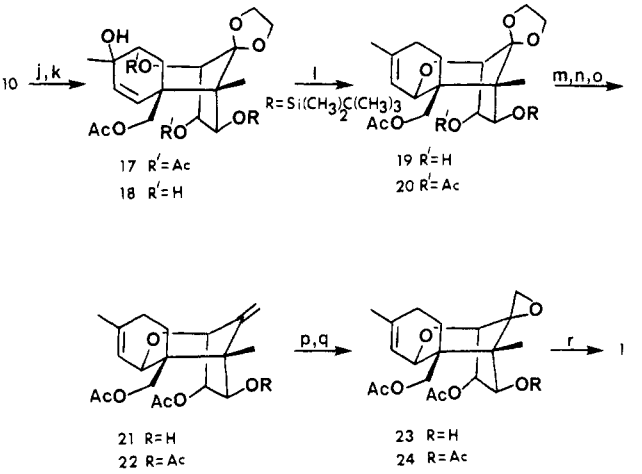


[a] $CH(N(CH_3)_2)_3$ (3 equiv), 120 °C, 16 h, 99%. [b] HOAc, NaOAc, H_2O, room temperature, 1 h, 99%. [c] Methyl vinyl ketone, diisopropylethylamine, THF, room temperature, 96 h, 95%. [d] LDA (2 equiv), THF, −78 °C 1 h, 80%. [e] MsCl (3 equiv), imidazole (3 equiv), DMF, room temperature, 16 h, 80%. [f] CH_3Li (1 equiv), THF, −78 °C, 1 h, 90%. [g] Excess $LiAlH_4$, DME, reflux, 1 h, 75%. [h] TsOH (0.1 equiv), CH_2Cl_2, room temperature, 10 min, **11** (25%), **13** (65%). [i] TsOH (0.1 equiv), CH_2Cl_2, room temperature, 16 h, **13** (45%), **15** (30%).

exposure of **13** to the acidic conditions for 16 h at room temperature resulted in a 3:2 mixture of starting material and the oxetane **15**.[12] These results provide a interesting contrast to similar cyclizations in related systems lacking the C3 hydroxyl group.[10]

To circumvent the undesired cyclization of the C15 hydroxyl, the triacetate **17** was selectively hydrolyzed to the diol **18**, which readily cyclized upon acid treatment to give the trichothecene **19** as the sole product (see Scheme II). The ^1H NMR spectrum of the corresponding diacetate **20** confirmed the presence of a methyl-substituted olefin and acetates at C3 and C15 and showed a characteristic coupling between protons at C10 and C11 observed in several natural trichothecenes.[13] The epoxide group was stereoselectively incorporated by a similar procedure to that first

Scheme II



[j] Ac_2O, C_5H_5N, room temperature, 16 h, 95%. [k] 2 M NH_4OH, CH_3OH, room temperature, 16 h, 70%. [l] TsOH catalyst, CH_2Cl_2, room temperature, 10 min, 90%; Ac_2O, C_5H_5N, room temperature, 16 h, 95%. [m] 1 N HCl, CH_3OH, room temperature, 48 h, 70%. [n] Methylenetriphenylphosphorane (1.5 equiv), THF, 60 °C, 1 h, 75%. [o] *n*-Bu_4NF (4 equiv), THF, room temperature, 4 h, 70%. [p] MCPBA (1 equiv), CH_2Cl_2, 0 °C, 2 h, 75%. [q] Ac_2O, C_5H_5N, room temperature, 16 h, 95%. [r] 2 M NH_4OH, CH_3OH, room temperature, 3 h, 65%.

used by Raphael and co-workers.[2a] Treatment of the hydroxy olefin **21** with *m*-chloroperbenzoic acid followed by acetylation gave triacetoxyscirpenol (**24**). Selective hydrolysis of the C3 acetate of **24** gave synthetic anguidine (**1**), which was confirmed by comparison with an authentic biosynthetic sample.[14]

Anguidine from natural sources has been extensively studied and chemically modified to provide other natural trichothecenes such as trichodermol (**2**) and verrucarol (**3**),[15] in addition to numerous derivatives.[16] This work therefore provides formal enantioselective syntheses of all these compounds, highlights the application of prochiral distinctions by microbial reduction as an efficient route to chiral starting materials for the synthesis of natural products, demonstrates preferred pathways of acid-catalyzed cyclizations of the A + C ring tetraol **10**, which have not been previously reported, and provides synthetic access to many interesting chiral intermediates for evaluation of biological activity and assessment of structure–activity relationships.

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Registry No. 1, 2270-40-8; **4**, 84736-14-1; **5**, 85925-72-0; **6**, 85925-73-1; **7**, 85925-74-2; **8**, 85925-75-3; **9**, 85925-76-4; **10**, 85925-77-5; **11**, 85925-78-6; **12**, 85925-79-7; **13**, 85925-80-0; **14**, 85925-81-1; **15**, 85925-82-2; **16**, 85925-83-3; **17**, 85925-84-4; **18**, 85925-85-5; **19**, 85925-86-6; **20**, 85925-87-7; **21**, 85925-88-8; **23**, 6121-60-4; **24**, 4297-61-4; $CH(N(CH_3)_2)_3$, 5762-56-1; methyl vinyl ketone, 78-94-4.

Supplementary Material Available: Listing of spectral data for selected pertinent compounds (4 pages). Ordering information is given on any current masthead page.

(11) The product ratio of **11** and **13** was variable depending on the type of acid catalyst, solvent, concentration, and temperature. We could not find conditions to give better than 50% of the trichothecene **11**. The structures were readily established by analysis of 470-mHz ^1H NMR spectra of the corresponding derivatives **12** and **14**, respectively.

(12) The structure of **15** was established by analysis of ^1H and ^{13}C NMR spectra of the corresponding diacetate **16**.

(13) A listing of spectral data for pertinent new compounds isolated and purified en route to anguidine are provided as supplementary material.

(14) (a) Biosynthetic anguidine (**1**) was donated by Dr. T. Doyle, Bristol Laboratories. (b) For reported physical properties and spectral data of **1** see ref 1d and 16 and references therein. (c) The ^{13}C NMR spectrum of **1** is reported in the following: Ellison, R. A.; Kontsonis, F. N. *J. Org. Chem.* **1976**, *41*, 576.

(15) Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.* **1980**, *21*, 4549.

(16) Kaneko, T.; Schmitz, H.; Essery, J. M.; Rose, W.; Howell, H. G.; O'Herron, F. A.; Nachfolger, S.; Huftalen, J.; Bradner, W. T.; Partyka, R. A.; Doyle, T. W.; Davies, J.; Cundliffe, E. *J. Med. Chem.* **1982**, *25*, 579.