19 and 20, the $W_{1/2}$ of the ^{33}S absorption responds to changes in the solvent environment. The band width is directly related to the correlation time, which can be factorized into the components: molecular size, solution viscosity, and symmetry.[5] On the basis of the solvent dependence of $W_{1/2}$ for both 19 and 20, it appears that the rotational motions of these sulfones are more restricted in chloroform and dimethyl sulfoxide solvents than in acetone and methanol, which is probably related to the magnitude and degree of intra- and intermolecular hydrogen bonding. Comparisons of the $W_{1/2}$ for sulfones 1–6 illustrates the relationship between molecular size and correlation times for simple dialkyl sulfones.

Acknowledgment is made to the Department of Energy (Contract DE-A505-80ER10641) and the University of North Carolina for support of this research. The Bruker WM-250 NMR spectrometer was purchased from a grant from the National Science Foundation (CHE-79-12130). We are grateful to Dr. Clifford Venier of Iowa State University for his suggestions and valuable input. We are grateful to Professors Robert L. McKee and Paul J. Kropp for homogeneous samples of sulfones.

Registry No. 1, 67-71-0; 2, 597-35-3; 3, 595-50-6; 4, 1886-75-5; 5, 598-03-8; 6, 598-04-9; 7, 127-63-9; 8, 599-66-6; 9, 80-09-1; 10, 620-32-6; 12, 4988-33-4; 13, 126-33-0; 14, 77-79-2; 15, 6522-45-8; 16, 107-61-9; 17, 82338-32-7; 18α, 70332-86-4; 18β, 70355-05-4; 19, 82338-33-8; 20, 82338-34-9; ^{33}S, 14257-58-0.

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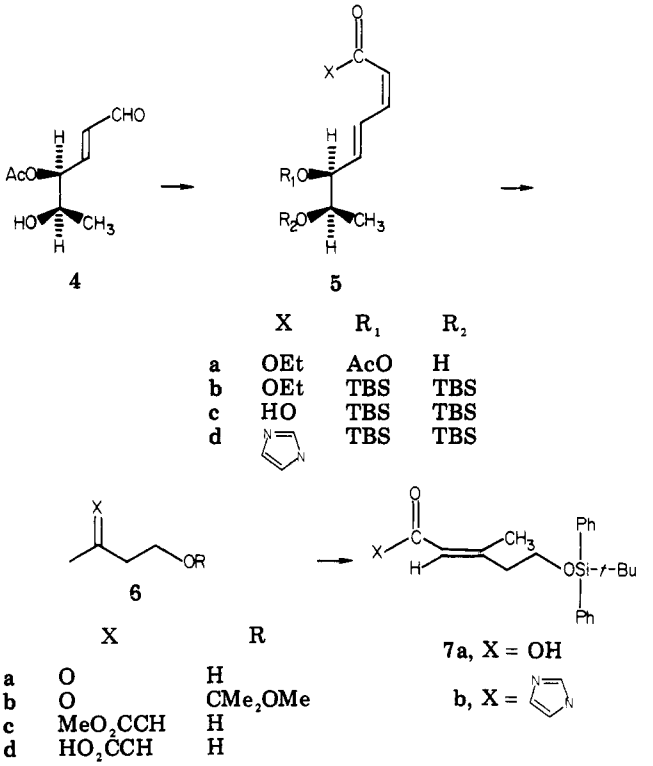
Synthesis of Trichoverrin B and Its Conversion to Verrucarin J

Summary: Anguidine (**3b**) was converted to verrucarol (**3a**), which in turn was selectively acylated to yield trichoverrin B (**2**). Trichoverrin B reacts with pyridinium dichromate in dimethylformamide, via a novel oxidative ring closure, to give verrucarin J (**11a**) in 50% yield.

Sir: Recently the isolation and characterization of the trichothecenes trichoverrins A (**1**) and B (**2**) from *Myrothecium verrucaria* was reported.[1] These compounds contain all the functionality characteristic of the macrocyclic roridins[2] and baccharins[3] except that the macrocyclic ring is broken. We now report the synthesis from verrucarol (**3a**) of trichoverrin B (**2**) and its conversion into verrucarin J (**11a**) via a novel oxidative ring closure. Since the total synthesis of verrucarol (**3a**) has recently been reported,[4] this work constitutes a formal total synthesis of these two trichothecenes. While this work was in progress, other procedures for acylating verrucarol were reported from the laboratories of Still[5] and White;[6] previous work by Tamm[7] in this area must also be noted.

Scheme I



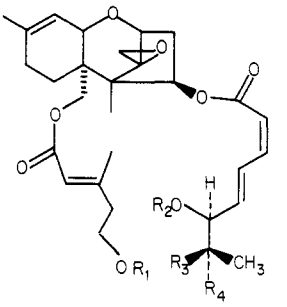
4 5

	X	R_1	R_2
a	OEt	AcO	H
b	OEt	TBS	TBS
c	HO	TBS	TBS
d		TBS	TBS

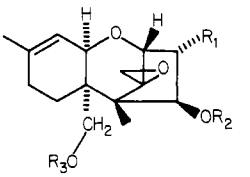
6

	X	R
a	O	H
b	O	CMe_2OMe
c	MeO_2CCH	H
d	HO_2CCH	H

7a, X = OH
b, X =



	R_1	R_2	R_3	R_4
1	H	H	H	OH
2	H	H	OH	H
10	DPS	TBS	TBSO	H



3a, $R_1 = R_2 = R_3 = H$
b, $R_1 = OH$; $R_2 = R_3 = Ac$
c, $R_1 = OC(=S)OPh$; $R_2 = R_3 = Ac$
d, $R_1 = H$; $R_2 = R_3 = Ac$
e, $R_1 = R_2 = H$; $R_3 = Ac$

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(2) (a) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 61. (b) Tamm, C. In "Mycotoxins and Human and Animal Health"; Rodricks, J. V., Hesseltine, C. W., Mehlman, M. A., Eds.; Pathotox Publishers: Park Forest South, IL, 1977; p 209. (c) Tamm, C.; Breitenstein, W. In "The Biosynthesis of Mycotoxins, A Study in Secondary Metabolism"; Steyn, P. S., Ed.; Academic Press: New York, 1980; p 69.

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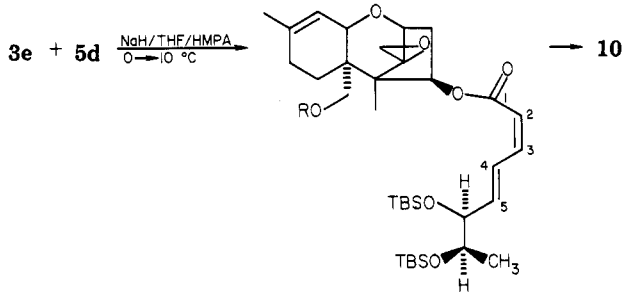
(7) (a) Breitenstein, W.; Tamm, C. *Helv. Chim. Acta.* **1978**, *61*, 1975. (b) Notegen, E.-A.; Toni, M.; Tamm, C. *Ibid.* **1981**, *64*, 316. (c) This group has just reported the synthesis of verrucarin A and 3α-hydroxyverrucarin A: Mohr, P.; Toni, M.; Grossen, P.; Herold, P.; Tamm, C. *Ibid.*, in press.

0022-3263/82/1947-3358$01.25/0

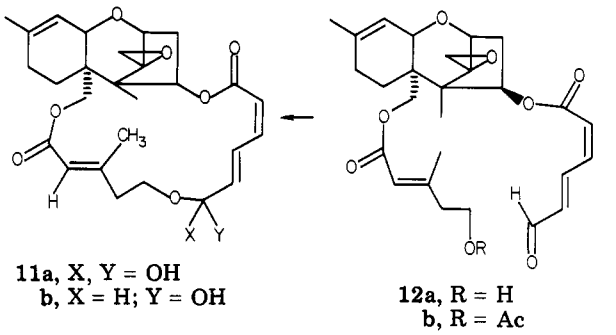
Scheme II



8a, R = Ac
b, R = H
(E 4/5)

9, R = Ac
(Z 4/5)

Scheme III



11a, X, Y = OH
b, X = H; Y = OH

12a, R = H
b, R = Ac

Verrucarol (**3a**) was prepared from anguidine (**3b**) by a modification[8] of our earlier procedure.[11] The dienic acid side chain **5c** was synthesized as outlined in Scheme I. Reaction of the unsaturated aldehyde **4**[12] with ethyl (trimethylsilyl)acetate (LDA/THF/−78 °C) gave ester **5a** and its *E* isomer in 2:1 ratio. After solvolysis (MeOH/NaOMe) which removed the acetate group but left unchanged the ethyl ester function and subsequent silyation with *tert*-butyldimethylsilyl chloride (TBS; DMF, imidazole), the *Z* isomer **5b** was obtained by silica gel chromatography (45% yield from aldehyde **4**). Saponification (LiOH/DME/H_2O) then afforded the acid **5c** as a crystalline solid, mp 77–79 °C.[13]

The acrylic acid side chain **7a** was synthesized from 3-oxo-1-butanol (**6a**;[14] scheme I) by first protection of the alcohol as the ketal **6b** (2-methoxypropene/TsOH/THF) and olefination [methyl (trimethylphosphoryl)acetate/NaH/DME] followed by acid hydrolysis to give **6c** (62% yield from **6a**) as a 1:5 mixture of *Z* and *E* isomers, respectively.[15] Saponification of **6c** with sodium hydroxide in water followed by acidification gave the acid **6d** (75%). Treatment with *tert*-butyldiphenylsilyl chloride and hydrolysis of the silyl ester (LiOH/DME/H_2O) followed by column chromatography and crystallization from methanol–water gave the pure *E* acid **7a** (81% yield), mp 104.5–105 °C.

A number of methods[16] were tried, without success, to attach the side chains to verrucarol or its monoacetate. Reaction of 15-acetylverrucarol **3e** with sodium hydride in THF containing 1% HMPA followed by the addition of the imidazolide **5d**[17] at −10 °C (Scheme II) gave a 1:1 mixture of **8a** and **9** in 54% yield. HPLC fractionation and saponification (LiOH/DME/H_2O) gave the alcohol **8b** (91%).

Use of the reaction conditions described above failed to effect esterification of the alcohol **8b**. However, if the material was treated with sodium hydride and *n*-Bu_4NI in THF and then allowed to react with the imidazolide **7b**[17] at room temperature, the diester **10** (60%) and unreacted **8b** were isolated. Extended reaction times and/or higher temperatures did not improve the yield of this reaction. Desilylation (*n*-Bu_4NF) gave trichoverrin B (60%), identical in all respects with the natural material.

Attention was now turned to closure of the macrocyclic ring to give verrucarin J (**11a**; Scheme III). Sodium periodate oxidation of trichoverrin B[18] (**2**) in aqueous acetone gave the aldehyde **12a**. It was hoped that **12a** would cyclize to the hemiacetal **11b**, and oxidation with manganese dioxide would give verrucarin J (**11a**). However, after 3 weeks at room temperature in dimethoxyethane, no reaction of **12a** was observed. Therefore, attempts, were made to oxidize the aldehyde **12a** to the carboxylic acid in order to effect macrolactonization. However, a variety of oxidation procedures caused decomposition or cleavage of the dienic ester side chain.

In our laboratories, pyridinium dichromate (PDC)[19] has been an effective oxidant of hemiacetals to give lactones.[20] When the aldehyde **12a** was treated wth PDC, verrucarin J (**11a**) was, in fact, formed. The reaction would appear to involve oxidation of the ring-closed hemiacetal **11b**.

PDC has been shown to convert roridins into verrucarins in high yield.[21] It seemed likely that PDC oxidation of the trichoverrins would result in a similar cleavage to give the aldehyde **12a**, which would be oxidized in situ by PDC to give verrucarin J (**11a**). When trichoverrin B (**2**) was treated with PDC in DMF, a mixture of the aldehyde **12a** and verrucarin J (**11a**) did form. After the reaction mixture stood at room temperature for 3 days, verrucarin J (**11a**) was isolated from the mixture in 50% yield.

Acknowledgment. This investigation was supported by Grants No. CA 25967 (B.B.J.) and CA 28192 (B.F.-R.), awarded by the National Cancer Institute, DHHS.

Registry No. **2**, 82495-56-5; **3a**, 2198-92-7; **3c**, 82510-84-7; **3e**, 2198-94-9; **4**, 76739-67-8; (*Z*)-**5a**, 82495-45-2; (*E*)-**5a**, 82495-46-3;

(8) Treatment of anguidine with phenyl thiocarbonate, pyridine, and a catalytic amount of (dimethylamino)pyridine in methylene chloride according to the Robins variation[9] of the Barton–McCombie deoxygenation[10] gave the thiocarbonate **3c**. This substance was then cleanly reduced to the diacetate **3a** (80%) by treatment with tri-*n*-butylstannane in benzene containing a catalytic amount of α,α-azobis(isobutyronitrile) under argon. Transesterification with sodium methoxide in methanol gave verrucarol as previously described.[11] Selective access to the secondary hydroxyl group was accomplished by the selective acetylation of the primary hydroxyl group with acetic anhydride and pyridine to give **3e**.[11]

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(13) This compound gave satisfactory elemented analysis and/or high-resolution MS data and IR and 200-MHz NMR spectra.

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(15) The ratio of *E* and *Z* isomers produced in the olefination was dependent on the nature of the protecting group. With the unprotected alcohol, **6a**, the ratio was 2:1 and with its THP derivative, 1:2. The *tert*-butyldiphenylsilyl derivative failed to react.

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(17) The imidazolides **5d** and **7b** were synthesized from the corresponding acids by treatment with carbonyldiimidazole in THF at room temperature in 89% yields and quantitative, respectively.

(18) Trichoverrin B used in these reactions was isolated from large-scale fermentation of *Myrothecium verrucaria*.[1a]

(19) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(20) Dawe, B.; Fraser-Reid, B., unpublished data.

(21) Jarvis, B. B.; Midiwo, J. O.; Flippen-Anderson, J. L.; Mazzola, E. P. *J. Nat. Prod.*, in press.

(Z)-5b, 82495-47-4; 5c, 82495-48-5; 5d, 82495-52-1; 6a, 590-90-9; 6b, 82495-49-6; (Z)-6c, 32775-50-1; (E)-6c, 35066-36-5; (Z)-6d, 17880-06-7; (E)-6d, 19710-84-0; (E)-7a, 82495-51-0; 7b, 82495-54-3; 8a, 82495-53-2; 8b, 82495-55-4; 9, 82535-99-7; 10, 82521-42-4; 11a, 4643-58-7; 12a, 82495-57-6; ethyl trimethylsilyl acetate, 4071-88-9; methyl trimethylphosphorylacetate, 82495-50-9; anguidine, 2270-40-8; phenyl thiocarbonate, 82495-44-1; verrucarol, 2198-92-7.

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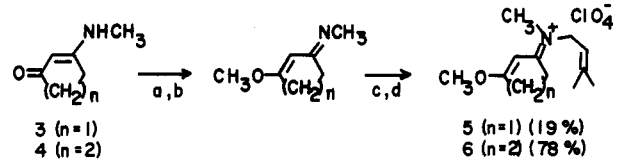
Electron-Transfer-Initiated Iminium Salt Photospirocyclization Methodologies. Model Studies for Harringtonine Alkaloid Synthesis

Summary: Conjugated iminium salts, derived by O-alkylation or O-acylation of *N*-allyl β-enaminones, undergo electron-transfer-initiated photocyclization reactions leading to the production of spirocyclic amines. The yields of these processes are exceptionally high when the allyl grouping of the salts possess (trimethylsilyl)methyl substitution. Model studies have demonstrated the utility of these spirocyclization reactions in synthetic approaches to the Harringtonine alkaloids.

Sir: During the past decade, a large effort has been expended to probe the details of organic photochemical processes proceeding by one-electron-transfer mechanisms.[1] Our recent investigations in this area have focused on the electron-transfer-initiated, excited-state reactions of compounds containing the iminium salt ($R_2C{=}N^+R_2$) grouping.[2] We have shown that the excited states of these systems participate in reaction pathways induced by one-electron transfer from a variety of neutral donors, including olefins, ethers, and aromatic hydrocarbons. In the cases investigated, the nature of the processes followed appear to be controlled by the chemistry of the donor-derived cation radical intermediates. Equations 1–3 summarize the types of carbon–carbon bond-forming reactions that occur in these systems as a result of nucleophilic addition to and deprotonation or desilylation of the initially formed radical cation intermediates.

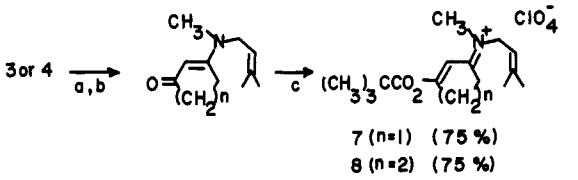
Results from prior studies in this area have demonstrated that *N*-allyliminium salt photocyclization reactions, occurring by intramolecular pathways analogous to that shown in eq 1, serve as useful methods for construction of pyrrolidine-ring-containing heterocycles.[2b] The structural outcomes and modest yields of these processes suggested their potential application in synthetic routes for construction of complex natural product structures. This feature is currently being explored in efforts directed at the development of spirocyclization methodologies that can be employed in the synthesis of members of the harringtonine alkaloid family of general structure **2** (R = acyl).[3]

Scheme I[a]



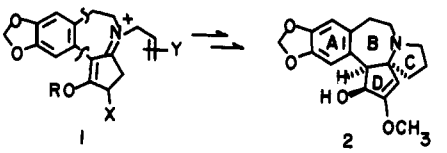
[a] (a) CH_3I, (b) 10% NaOH, (c) $(CH_3)_2C{=}CHCH_2Br$, (d) Dowex, ClO_4^- form.

Scheme II[a]



[a] (a) *n*-BuLi, (b) $(CH_3)C{=}CHCH_2Br$, (c) $AgClO_4$, $(CH_3)_3CCOCl$.

Accordingly, photocyclization of the *N*-allyliminium salt grouping found in O-protonated, -alkylated, or -acylated β-enaminones **1** will be used to introduce the spirocyclic CD ring unit of the target systems. In this communication we report the results of model studies that show that this photochemical method is compatible with the functionality and structural requirements of approaches to **2** via salts related to **1**.



1 **2**

Initial studies were conducted to determine if the iminium cation chromophore found in salts **1** would participate in electron-transfer-induced photocyclization reactions like those observed earlier with phenyl conjugated systems.[2a,d] For this purpose, a series of *N*-prenyliminium perchlorates **5-8** were prepared from β-enaminone precursors by the routes outlined in Schemes I and II. The *N*-prenyl side chain was incorporated into the systems selected for initial study in order to guarantee efficient electron transfer between the olefin and excited iminium salt groups.[4] Irradiation of methanolic solutions of iminium perchlorates **5-8**, conducted in a preparative apparatus with light of $\lambda > 240$ nm, followed by aqueous base treatment of the crude photolysate and chromatographic purification on alumina or silica gel, afforded the spirocyclic amines **9-12** as mixtures of C-8 and C-9 epimers in the yields ranging from 19% to 31%. The O-protonated salt **14**, prepared in situ by treatment of a methanolic solution of the corresponding enaminone with 0.1 N

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(4) (a) Electron-transfer rates are dependent upon the donor olefin oxidation potentials ($F_{1/2}(+)$) and acceptor excited iminium salt reduction potentials ($E_{1/2}(-)$) and singlet energies ($\Delta E_{0,0}$) as discussed by Weller.[4b] From UV-absorption spectroscopic data and known reduction potentials of analogous systems,[4c] we estimate that the $\Delta E_{0,0}$ and $E_{1/2}(-)$ for the chromophore present in these iminium salts are ca. 80 kcal/mol and ca. −1.5 eV, respectively. Thus, $E_{1/2}(+)$ for olefins must be below ca. +2.0 to insure efficient electron transfer. (b) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259. (c) Andrieux, C. P.; Saveant, J. M. *J. Electroanal. Chem.* **1970**, *26*, 223.

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