trichoverrins lie along the biosynthetic pathway to the macrocyclic trichothecenes. There are a number of details yet to be worked out including the point at which further elaboration of the double bond in the C-15 ester group occurs and at which point on the biosynthesis path the roridins and verrucarins diverge. The discovery of the role played by the trichoverrins in the biosynthesis of the macrocyclic trichothecenes suggests that conversion of verrucarol[19] to the highly biologically active macrocyclic trichothecenes via trichoverrins is a viable synthetic route. These and other aspects of this work currently are under investigation.

Acknowledgment. This investigation was supported by Grant Number CA 259667-01, awarded by the National Cancer Institute, DHHS. G. P. Stahly thanks Gillette Corporation for a fellowship. We thank Dr. Gary McCluskey of the Frederick Cancer Research Center, Frederick, MD, for mass spectral measurements.

(17) This experiment was repeated by using a mixture of [^{14}C]trichoverrin A and B (1 mg in 20 mL of culture).[18] The crude fermentation extract was subjected to TLC followed by autoradiographic analysis of the plate. A number of radioactive bands corresponding in descending order in R_f to verrucarins A, B, and J, isororidin E, and roridin A were clearly evident. Although this experiment supports the conclusions drawn from the preparative experiment, use of specifically labeled trichoverrin would yield a more definitive result.

(18) These experiments used ^{14}C-labeled trichoverrins synthesized by feeding ^{14}C-labeled sodium acetate to a culture of *M. verrucaria* (ATCC No. 24571). The experiments involving the biotransformations of **9** and **10** were conducted with a mutant strain of *M. verrucaria* developed by UV irradiation of the fungus obtained from the American Type Culture Collection; for details see G. Pavanasasivam, Ph.D. Thesis, University of Maryland, 1980.

(19) Readily available anguidine[1] has been transformed in high yield to verrucarol: see Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.*, in press.

A Synthetic Route to the C4 Octadienic Esters of Trichothecenes from D-Glucose

Deen Bhandu Tulshian† and Bert Fraser-Reid*

Guelph-Waterloo Centre for Graduate Work in Chemistry
University of Waterloo
Waterloo, Ontario, Canada N2L 3G1

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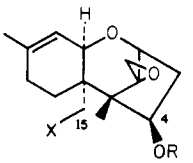
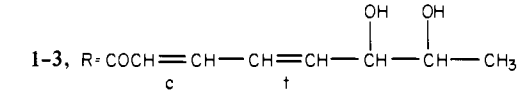
Considerable attention is currently focused upon the trichothecene family of sesquiterpenes owing, in part, to the wide range of biological activities displayed by this group of natural products.[1,2] This is particularly true for the macrocyclic members in which an intricate concentration of ether–ester–olefin–alcohol functionalities connects the C4 and C15 hydroxyl groups of the tricyclic backbone. Changes in the type and/or orientation of the functionalities elicit profound biological effects, judging from the wide spectrum of activities found in the various verrucarins and roridins.[2] Impressive gains in synthetic methodology relating to the tricyclic backbone have been reported[3] but, by contrast, there have been no reports concerning the components of the macrocyclic "ribbon".

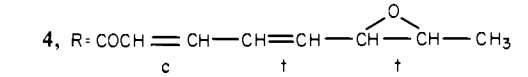
Impetus for appropriate methodology comes from the work of Jarvis et al. in the preceding communication, describing the novel esters, trichodermadinediols A and B (**1A** and **1B**), trichoverrols A and B (**2A** and **2B**), and trichoverrins A and B (**3A** and **3B**).[4]





1-3, R = COCH=CH—CH=CH—CH(OH)—CH(OH)—CH$_3$ (c, t)

1, (A and B) X = H
2, (A and B) X = OH
3, (A and B) X = OCOCH=C(CH$_3$)–(CH$_2$)$_2$OH (*E*)



4, R = COCH=CH—CH=CH—CH(O)—CH—CH$_3$ (c, t, t)

4, X = H

c = cis, t = trans

These "incomplete macrocycles", **1–3**, are reminiscent of trichodermadiene (**4**) reported earlier from the same laboratory.[5] The characterization undertaken by these workers revealed only the gross structures of the C4 esters. In this communication we outline a simple synthetic program that establishes structural details of the pendant C4 esters in **1–4** and which makes this class of dienic esters available with control of chiral as well as geometric centers.

Our synthetic approach (Scheme I) emanated from previous work in our laboratory which showed that triacetyl-D-glucal **5a** was converted into a mixture of pseudoglucal **6a** and the hydroxy aldehyde **7a** upon treatment with boiling water.[6,7] These substances are readily separated, but fractionation is unnecessary, since free-radical scavengers or darkness suppresses the formation of **7a**.[6] On the other hand, the excellent procedure of Perlin and co-workers affords **7a** in virtually quantitative yield,[8] an encouraging circumstance since the contiguous ene–diol moiety of **7** permits a synthesis that determines the stereochemistries, *absolute and relative*, of the C4 esters of compounds **1–4**.

Accordingly triacetyl-D-glucal[9] (**5a**) was converted into the 6-deoxy analogue **5b** (four steps in 51% overall yield),[10] which was subjected to the Perlin transformation,[8] whereby **7b** was obtained in 95% yield. In a similar way, triacetyl-D-galactal **8**[12] was converted into the D-threo analogue **9**.

A number of procedures for obtaining the dienic esters were tested on the aldehyde **7a** and the results, which are shown in Table I, speak for themselves. With regard to the desired cis,trans isomer **11**, the best procedure (entry 2) was found to be that of Peterson,[13] while the Horner–Emmons reagent (entry 1) used with such success in Kishi's laboratory[14] was very disappointing. Similarly the aldehydes **7b** and **9** were converted into the isomers **13a** and **14a**, respectively, which were deacetylated to **13b** and **14b** with sodium methoxide.[11]

The optical rotations of the dienes **13b** and **14b** being −42.06° and −48.00° are uncomfortably close, but fortunately their NMR

† Holder of a Graduate Fellowship (University of Maryland) awarded by The Upjohn Company, Kalamazoo, Michigan.

* Please address correspondence to this author at the Department of Chemistry, University of Maryland, College Park, MD 20742.

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(9) Tri-*O*-acetyl-D-glucal, **5a**, is obtainable from Pfanstiehl Laboratories, Waukegan, IL.
(10) For preparation of **5b**, **5a** was treated as follows: (i) NaOMe/MeOH; (ii) TsCl/pyridine/0 °C/48 h followed by Ac_2O; (iii) NaI; (iv) *N*-Bu_3SnH.
(11) All new compounds gave satisfactory NMR, UV, and IR spectra and elemental analysis and/or high-resolution MS.
(12) Tri-*O*-acetyl-D-galactal, **8**, is obtainable from Raylo Chemicals, Edmonton, Alberta, Canada.
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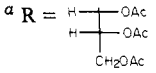
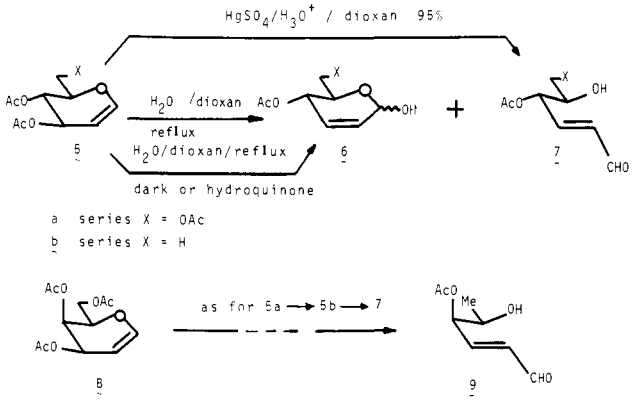
Table I. Conversion of 7a into Conjugated Dienic Esters

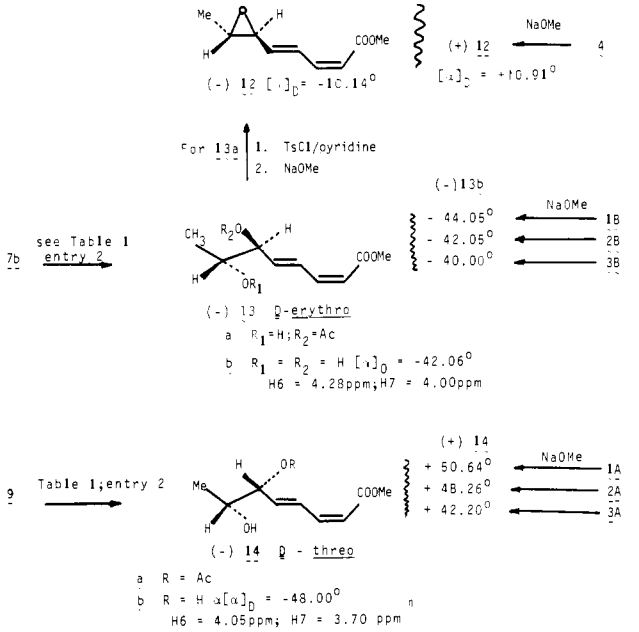
entry	reagents	products, % relative yields: R, COOMe (10^a)	products, % relative yields: R, COOMe (11^a)
(1)			
(1)	$(EtO)_2P-CH_2CO_2Me/NaH/Et_2O/-78$ °C	100	0
(2)	Me_3SiCH_2COOMe/n-BuLi/-78 °C/5 min	50	50
(3)	$Ph_3P=CHCOOMe/MeOH$/room temperature/3 h	~65	~35
(4)	$Ph_3P=CHCOOMe/CH_3CN$	~80	~20

[a] R = 

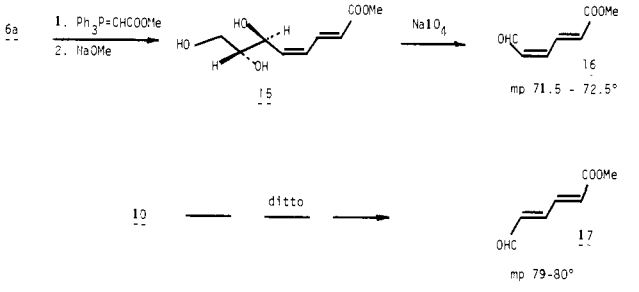
Scheme I



Scheme II



Scheme III



parameters, particularly the chemical shifts for H6 and H7, as shown in Scheme II, allow for a clear assignment of relative stereochemistry, erythro versus threo, respectively.

On the basis of the foregoing, the six trichothecenes (**1A**, **1B**, **2A**, **2B**, **3A**, and **3B**) were each treated with a catalytic amount of sodium methoxide in methanol. The resulting dienic esters were isolated by preparative layer chromatography (10% $CHCl_3$ in MeOH), and erythro or threo configuration was assigned to each by comparing their NMR parameters with those of **13b** and **14b**. Their optical rotations were then determined to see whether the diol entity was of D or L configuration. From these analyses we conclude that the esters from the B group of **1**, **2**, and **3** all have D-erythro stereochemistries while those from the A group are all L-threo.

The intermediate **13a** also allows us to establish the absolute configuration of the epoxy ester from trichodermadiene (**4**). Thus, treatment of **13a** with *p*-toluenesulfonyl chloride and then with sodium methoxide afforded the oxirane (−)-**12**.[11] Methanolysis of **4** led to the dextrorotatory enantiomer.

Hydrolysis of the verrucarins gives *cis,trans*-muconic acid, and a ready[15] route to *cis,trans*-muconates is available from these intermediates (Scheme III). Thus, Witting reaction of **6a** followed by brief[16] methanolysis gives **15** which is cleaved by sodium periodate to give the crystalline aldehydic ester **16**.[11] Similarly **10** affords **17**.[11] An attractive feature of **16** and **17** is the differentiation of the termini which enables specific reactions to be undertaken at either end.

The differences in absolute configuration at C6′ and C7′ of the dienic esters of the trichothecenes **1**–**4** are intriguing, and it will be of interest to determine their importance for the biosynthesis and pharmacology of these compounds. Experiments bearing on these aspects are currently under way.

Acknowledgment. We are grateful to Natural Sciences and Engineering Research Council of Canada and the Upjohn Company for financial assistance.

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